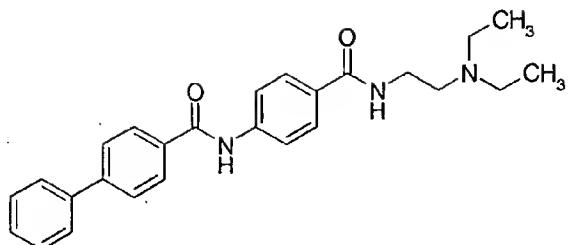


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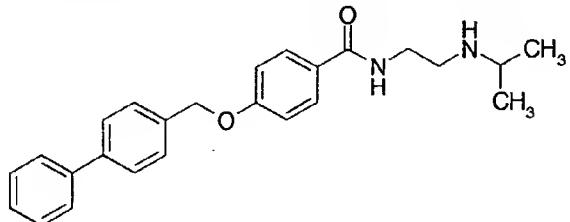
100



Oxalyl chloride (0.46 ml) and DMF (1 drop) were added to THF solution (15 ml) of 4-biphenylcarboxylic acid (0.879g) under ice-cooling. The reaction mixture was 5 stirred at room temperature for 30 minutes, and concentrated. The residue was dissolved in THF (10 ml), which was added dropwise to THF (20 ml) suspension of procaineamide hydrochloride (1.078 g) and triethylamine (1.4 ml) at 0°C. After stirring at 0°C for 30 minutes, 10% aqueous potassium carbonate solution was added to the 10 reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using 15 methanol to give the titled compound (1.147 g).  
Melting point: 237 - 240°C (decomposition)

## Reference Example 19

4-(4-Biphenylmethoxy)-N-[2-(isopropylamino)ethyl]benzamide  
20



WSC (0.708 g), HOBT (0.521 g), N-isopropyl ethylenediamine (0.353 g) and triethylamine (1 ml) were added to a mixed solution of 4-(4-biphenylmethoxy) 25 benzoate (1.007 g) in THF (30 ml) and acetonitrile (30 ml). After stirring at room temperature for 18 hours, water was added to the reaction mixture, and extraction was conducted

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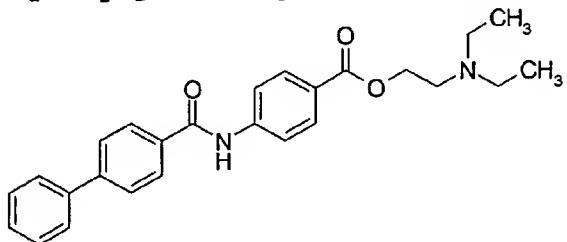
using ethyl acetate. The organic layer was washed with 10% aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried, and then concentrated.

The residue was recrystallized using ethanol to give the 5 titled compound (0.806 g).

Melting point: 150 - 154°C

Reference Example 20

10 2-(N,N-Diethylamino)ethyl 4-(4-biphenylylcarbonylamino)benzoate



Oxalyl chloride (0.39 ml) and DMF (1 drop) were added to THF solution (15 ml) of 4-biphenylylcarboxylic acid (1.091 g) under ice-cooling, which was stirred at room 15 temperature for 30 minutes, and concentrated. The residue was dissolved in THF (10 ml), which was added dropwise to THF suspension (30 ml) of procaine hydrochloride (1.091 g) and triethylamine (0.67 ml) at 0°C. After stirring at 0°C for 30 minutes, 10% aqueous potassium carbonate was added 20 to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using ethyl acetate/hexane to give the titled compound (0.728 g).

25 Melting point: 146 - 149°C

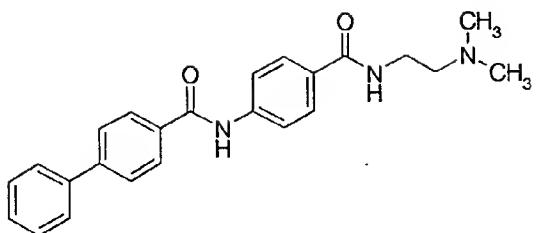
Reference Example 21

N-[4-[[[2-(Dimethylamino)ethyl]amino]carbonyl]phenyl] 4-biphenylylcarboxamide

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WSC (0.248 g), HOBt (0.156 g), N,N-dimethyl ethylenediamine (0.097 g) and triethylamine (0.21 ml) were added to a mixed solution of 4-(4-biphenylcarbonylamino)benzoate (0.323 g) in THF (15 ml) and acetonitrile (15 ml). After stirring at room temperature for 18 hours, water was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with 10% aqueous potassium carbonate and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using methanol/diethyl ether to give the titled compound (0.100 g).

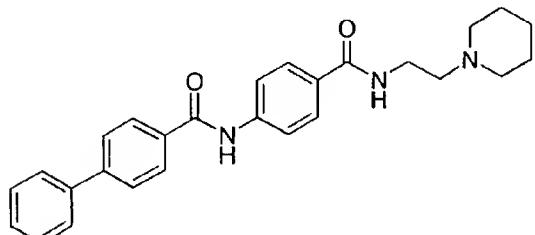
Melting point: 261 - 264°C (decomposition)

15

The compounds described in the following Reference Examples 22 to 25 were produced in the same manner as in Reference Example 21.

20 Reference Example 22

N-[4-[(2-(Piperidinoethyl)amino]carbonyl]phenyl] 4-biphenylcarboxamide



Melting point: 247 - 252°C (decomposition)

25

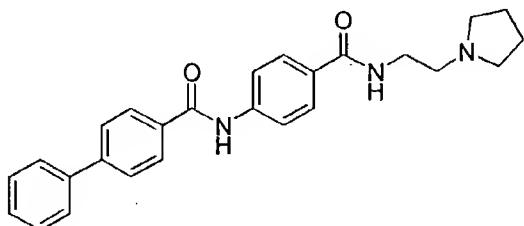
Reference Example 23

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**N-[4-[[2-(1-Pyrrolidinyl)ethyl]amino]carbonyl]phenyl]-4-biphenylylcarboxamide**

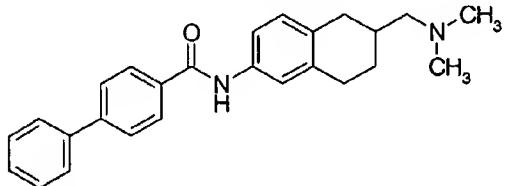


Melting point: 241 - 245°C (decomposition)

5

**Reference Example 24**

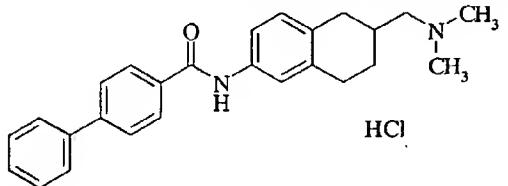
**N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-4-biphenylylcarboxamide**



10 Melting point: 164 - 166°C

**Reference Example 25**

**N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-4-biphenylylcarboxamide hydrochloride**



15

Melting point: >250°C

$^1\text{H-NMR}$   $\delta$ : 1.24-1.54 (1H, m), 1.84-2.10 (2H, m), 2.20-2.50 (3H, m), 2.26 (6H, s), 2.79-3.01 (3H, m), 7.10 (1H, d,

J=8Hz), 7.28-7.54 (5H, m), 7.60-7.82 (5H, m), 7.94 (2H, d,

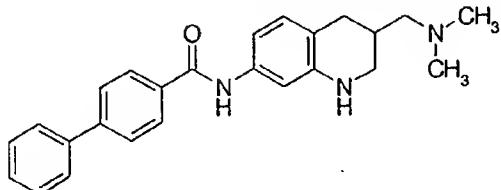
20 J=8Hz).

IR(KBr) 3028, 2910, 2640, 1658, 1538, 1417, 746, 701  $\text{cm}^{-1}$

**Reference Example 26**

**N-[3-[(N,N-Dimethylamino)methyl]-1,2,3,4-tetrahydronaphthalen-1-yl]-4-biphenylylcarboxamide**

## quinolinyl]-4-biphenylylcarboxamide

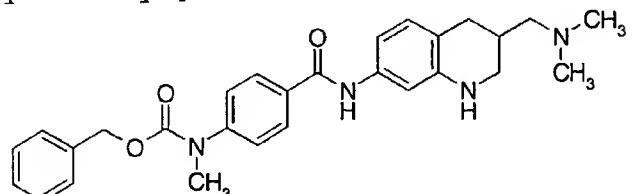


One drop of DMF was added to THF solution of 4-biphenylylcarboxylic acid (145 mg), and oxalyl chloride (0.1 ml) was added dropwise to the solution under ice-cooling, which was stirred at room temperature for 30 minutes. After the reaction mixture was concentrated, the residue was dissolved in THF (1 ml), which was added dropwise to pyridine solution (1.5 ml) of 7-amino-3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinoline (150 mg) under ice-cooling, and the reaction mixture was stirred for 30 minutes. After the temperature of the reaction mixture was raised to room temperature, 10% aqueous potassium carbonate was added to the reaction mixture, and extraction was conducted using a mixed solution of THF and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using THF-IPE to give the titled compound (180 mg).

Melting point: 206 - 211°C

## Reference Example 27

4-[N-[(Benzyoxy)carbonyl]-N-methylamino]-N-[3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahyd-7-quinolinyl]benzamide



One drop of DMF was added dropwise to THF solution (2

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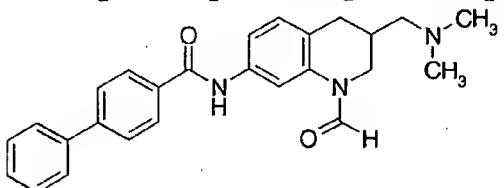
105

ml) of 4-[N-[(benzyloxy)carbonyl]-N-methylamino]benzoic acid (210 mg), and then oxalyl chloride (0.1 ml) was added dropwise under ice-cooling, which was stirred at room temperature for 30 minutes. After the reaction mixture was 5 concentrated, the residue was dissolved in THF (1 ml), which was added dropwise to pyridine solution (1.5 ml) of 7-amino-3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinoline (150 mg) under ice-cooling. The reaction mixture was then stirred for 30 minutes. After 10 the temperature of the reaction mixture was raised to room temperature, 10% aqueous potassium carbonate solution was added, and extraction was conducted using a mixed solution of THF and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, 15 dried, and then concentrated. The residue was recrystallized using THF-IPE to give the titled compound (220 mg).

Melting point: 167 - 172°C

20 Reference Example 28

N-[3-[(N,N-Dimethylamino)methyl]-1-formyl-1,2,3,4-tetrahydro-7-quinolinyl]-4-biphenylylcarboxamide



Anhydrous acetic acid (0.1 ml) was added to formic acid 25 (1 ml), which was stirred at 55°C for 2 hours. N-[3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydro-7-quinolinyl]-4-biphenylylcarboxamide (80 mg) was added to the reaction mixture under ice-cooling, which was stirred at room temperature for 72 hours. 10% aqueous potassium 30 carbonate solution was added to the reaction mixture to make the mixture alkaline, and extraction was conducted using ethyl acetate. The organic layer was washed with water and

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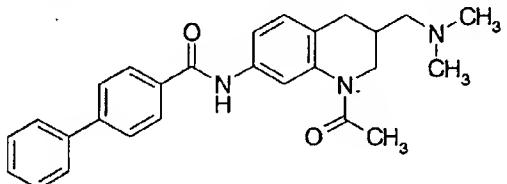
saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using THF-IPE to give the titled compound (80 mg).

Melting point: 134 - 138°C

5

Reference Example 29

N-[1-Acetyl-3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydro-7-quinolyl]-4-biphenylylcarboxamide

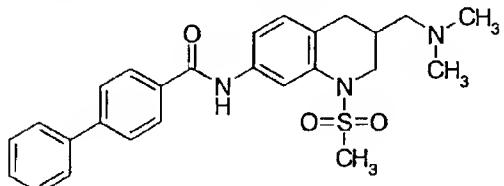


10 Acetyl chloride (0.02 ml) was added to pyridine solution (1 ml) of N-[3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydro-7-quinolinyl]-4-biphenylylcarboxamide (80 mg) under ice-cooling, which was stirred for 15 minutes, and then stirred at room temperature 15 for 15 minutes. 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using THF-IPE to give the titled compound 20 (64 mg).

Melting point: 167 - 173°C

Reference Example 30

25 N-[3-[(N,N-Dimethylamino)methyl]-1-methanesulfonyl-1,2,3,4-tetrahydro-7-quinolinyl]-4-biphenylylcarboxamide



Methanesulfonyl chloride (0.02 ml) was added to

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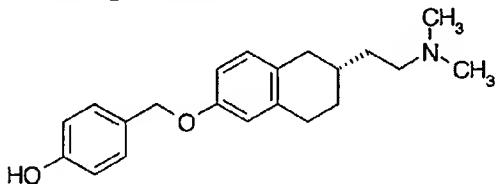
pyridine solution (1 ml) of N-[3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydro-7-quinolinyl]-4-biphenylcarboxamide (80 mg) under ice-cooling, which was stirred at room temperature for 1 hour. Further, 5 methanesulfonyl chloride (0.02 ml) was added to the reaction mixture under ice-cooling, which was stirred at room temperature for 12 hours. 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic 10 layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using THF-IPE to give the titled compound (64 mg).

Melting point: 184 - 188°C

15

Reference Example 31

2-(R)-[2-(N,N-Dimethylamino)ethyl]-6-(4-hydroxyphenyl)methoxytetralin



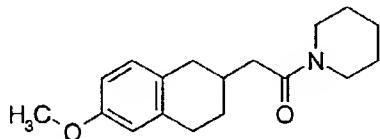
20 THF solution (2 ml) of 2-(R)-[2-(N,N-dimethylamino)ethyl]-6-[4-(4-methoxyphenylcarbonyloxy)phenylmethoxy]tetralin (330 mg) was added dropwise to THF suspension (4 ml) of lithium aluminum hydride (60 mg) under ice-cooling. 1N aqueous sodium hydroxide solution was 25 added to the reaction mixture to make the mixture basic, and the precipitate was removed by celite filtration. After the filtrate was concentrated, the residue was purified using silica gel chromatography (development solvent; ethyl acetate - methanol), and recrystallized (ethyl acetate-hexane) to give the titled compound (70 mg).

Melting point: 132 - 135°C

$[\alpha]_D^{20} = +56.9^\circ$  (c = 0.505, methanol)

## Reference Example 32

## 2-(6-Methoxy-2-tetralinyl)-1-piperidino-1-ethanone



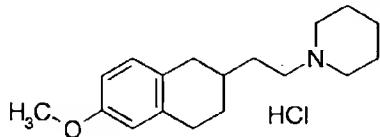
5        2-(6-Methoxy-2-tetralinyl)acetic acid (8.8 g) was dissolved in a mixed solution of THF (150 ml) and acetonitrile (50 ml), then piperidine (5.2 g), WSC (12 g), HOBT (6.0 g) and triethylamine (17 ml) were added to the solution, which was stirred at room temperature for 12  
10      hours. Water was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with 1N hydrochloric acid, water, saturated sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution, dried, and then  
15      concentrated. The residue was purified using silica gel chromatography (development solvent; ethyl acetate) to give the titled compound (10.3 g). Recrystallization from hexane gave crystals of the following melting points.

Melting point: 59 - 61°C

20

## Reference Example 33

## 6-Methoxy-2-(2-piperidinoethyl)tetralin hydrochloride



25      THF solution (50 ml) of 2-(6-methoxy-2-tetralinyl)-1-piperidino-1-ethanone (9.80 g) was added dropwise to THF suspension (100 ml) of lithium aluminum hydride (1.94 g) under ice-cooling. The temperature of the reaction mixture was raised to 60°C over 30 minutes, which was stirred for 30 minutes. After the reaction mixture was  
30      cooled to room temperature, 1N aqueous sodium hydroxide solution was added to make the reaction mixture basic, and

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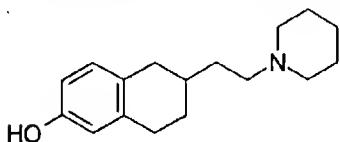
109

the precipitate was removed by celite filtration. The filtrate was concentrated and the residue was made into a hydrochloride, which was then recrystallized from ethanol-IPE to give the titled compound (9.80 g).

5 Melting point: 189 - 191°C

Reference Example 34

6-Hydroxy-2-(2-piperidinoethyl)tetralin



10 6-Methoxy-2-(2-piperidinoethyl)tetralin

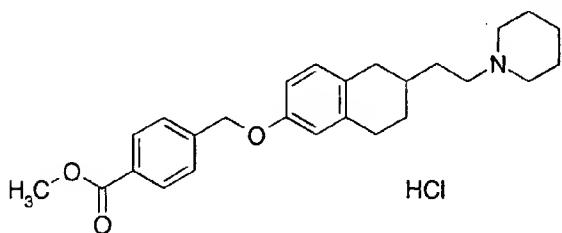
hydrochloride (9.3 g) was added to 48% hydrobromic acid (50 ml), which was refluxed with heating for 4 hours. After the reaction mixture was concentrated under reduced pressure, saturated sodium bicarbonate solution was added to the residue to make the water layer alkaline, and the water layer was extracted using a mixed solution of THF and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting crystal was washed with IPE to give the titled compound (5.8 g).

20 Melting point: 154 - 157°C

Reference Example 35

Methyl 4-[[2-(2-piperidinoethyl)-6-

25 tetralinyl]oxymethyl]benzoate hydrochloride



Diethyl azodicarboxylate (40% toluene solution, 5.10 g) was added dropwise to THF solution (15 ml) of 6-hydroxy-2-(2-piperidinoethyl)tetralin (1.50 g), methyl

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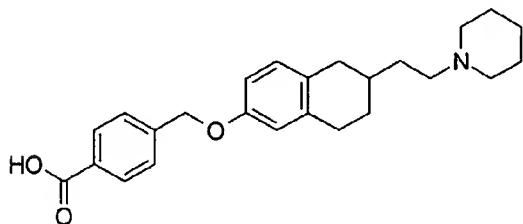
4-(hydroxymethyl)benzoate (1.44 g), and triphenylphosphine (2.60 g) at room temperature, which was stirred for 12 hours, and then concentrated. The residue was purified using aluminum column chromatography (development solvent; hexane ~ hexane:ethyl acetate = 15:1), which was made into a hydrochloride. The hydrochloride was recrystallized (methanol-IPE) to give the titled compound (1.36 g).

Melting point: 190 - 193°C.

10

## Reference Example 36

4-[[2-(2-Piperidinoethyl)-6-tetralinyl]oxymethyl]benzoic acid



15

3N Aqueous sodium hydroxide solution (1.8 ml) was added to methanol solution (20 ml) of methyl 4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzoate hydrochloride (1.06 g), which was refluxed with heating for 6 hours. After the reaction mixture was concentrated, water was added to the reaction mixture. Further, 1N hydrochloric acid was added to make the pH of the mixture about 7. The resulting crystals were filtered to give the titled compound (0.93 g). Recrystallization from ethanol gave crystals of the following melting points.

20

25

Melting point: 105 - 108°C

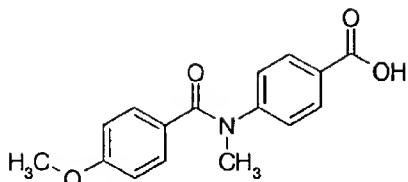
## Reference Example 37

4-[N-(4-Methoxybenzoyl)-N-methylamino]benzoic acid

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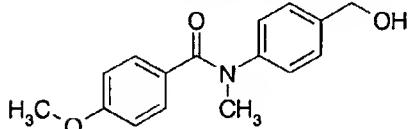
111



Aqueous solution (50 ml) of sodium carbonate (23 g) was added to THF solution (50 ml) of 4-(methylamino)benzoic acid (5.0 g), and p-anisoyl chloride (5.6 g) was added 5 dropwise to the solution under ice-cooling, which was stirred for 15 minutes, and then stirred at room temperature for 30 minutes. Concentrated hydrochloric acid was added to the reaction mixture under ice-cooling to make the water layer acidic, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using silica gel column chromatography (development solvent; hexane - 10 hexane:ethyl acetate = 1:2), and recrystallized (ethyl acetate-hexane) to give the titled compound (4.8 g).  
15 Melting point: 157 - 160°C.

## Reference Example 38

## N-[4-(Hydroxymethyl)phenyl]-4-methoxy-N-methylbenzamide



20 THF solution (1M, 16 ml) of borane was added dropwise to THF solution (10 ml) of 4-[N-(4-methoxybenzoyl)-N-methylamino]benzoic acid (1.14 g) under ice-cooling, which was stirred for 15 minutes, and then stirred at room 25 temperature for 1 hour. After water was added to the reaction mixture, 1N hydrochloric acid was further added, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated sodium bicarbonate, and saturated aqueous sodium chloride 30 solution, dried, and then concentrated. The residue was

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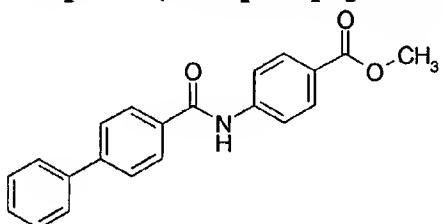
112

purified using silica gel chromatography (development solvent; hexane - hexane:ethyl acetate = 1:2), and recrystallized (ethyl acetate-hexane) to give the titled compound (770 mg).

5 Melting point: 85 - 90°C.

Reference Example 39

Methyl 4-(4-biphenylylcarbonylamino)benzoate

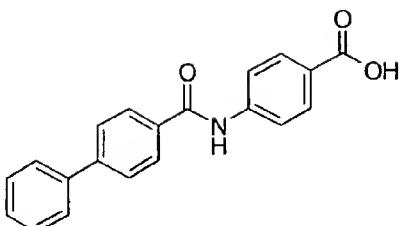


10 Oxalyl chloride (1.2 ml) and DMF (0.04 ml) were added to THF solution (30 ml) of 4-biphenylylcarboxylic acid (2.184g) under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes, which was concentrated. The residue was dissolved in THF (15 ml),  
15 which was added dropwise to THF solution (30 ml) of methyl 4-aminobenzoate (1.512 g) and triethylamine (2.1 ml) at 0°C. After the reaction mixture was stirred at 0°C for 30 minutes, 10% citric acid solution was added to the reaction mixture, and extraction was conducted using ethyl acetate.  
20 The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting crude crystal was washed with diethyl ether to give the titled compound (2.179 g).  
Melting point: 247 - 251°C.

25

Reference Example 40

4-(4-Biphenylylcarbonylamino)benzoic acid



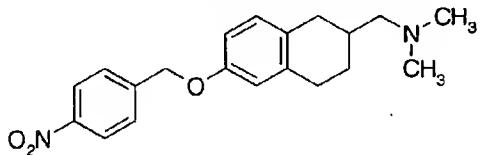
1N Aqueous sodium hydroxide solution (8 ml) was added to a mixed solution of methyl 4-(4-biphenylcarbonylamino)benzoate (1.998 g) in THF (60 ml) and methanol (20 ml), which was stirred at room temperature for 18 hours. 1N Hydrochloric acid (10 ml) was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting crude crystals were washed with diethyl ether to give the titled compound (1.760 g).  
Melting point: >320°C.

15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 7.37-7.57 (3H,m), 7.77 (2H,d), 7.85 (2H,d), 7.95 (4H,s), 8.08 (2H,d), 10.56 (1H,s)

16

#### Reference Example 41

2-[(N,N-Dimethylamino)methyl]-6-(4-nitrobenzyloxy)tetralin



20 Diethyl azodicarboxylate (40% toluene solution, 9.53 g) was added dropwise to THF solution (15 ml) of 2-[(N,N-dimethylamino)methyl]-6-hydroxytetralin (1.5 g), 4-nitrobenzylalcohol (3.35 g), and triphenylphosphine (5.74 g) at room temperature, which was stirred for 24 hours. The reaction mixture was concentrated, and the residue was purified using alumina column chromatography (development solvent; hexane ~ hexane:ethyl acetate = 8:1), and recrystallized (ethyl acetate-hexane) to give the titled compound (1.29 g).

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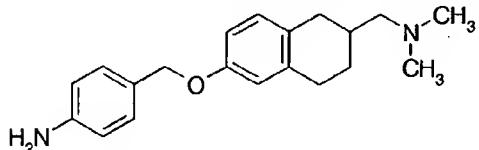
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Melting point: 83 - 89°C

## Reference Example 42

6-(4-Aminobenzyloxy)-2-[(N,N-dimethylamino)methyl]tetralin



After acetic acid (6 ml) was added to THF solution (12 ml) of 2-[(N,N-dimethylamino)methyl]-6-(4-nitrobenzyloxy)tetralin (1.91 g) under ice-cooling, zinc powder (3.67 g) was further added, which was stirred for 6 hours. The reaction mixture was filtered, and the filtrate was concentrated. 10% aqueous potassium carbonate solution and ethyl acetate were added to the residue, the precipitate was removed by celite filtration, and the filtrate was extracted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using aluminum column chromatography (development solvent; hexane ~ hexane:ethyl acetate = 4:1) to give the titled compound (1.05 g).

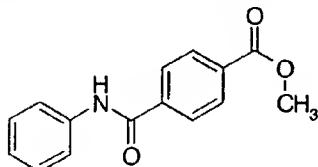
## Amorphous powder:

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.18-1.50(1H, m), 1.70-2.50(5H, m), 2.24(6H, s), 2.72-2.86(3H, m), 3.68(2H, brs), 4.88(2H, s), 6.58-6.82(4H, m), 6.99(1H, s), 7.14-7.30(2H, m).

25

## Reference Example 43

## Methyl 4-anilinocarbonylbenzoate



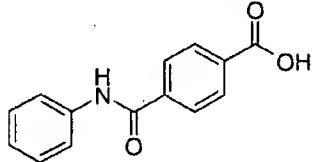
4-Methoxycarbonyl benzoic acid (540 mg), aniline (0.27 ml), WSC (863 mg) and triethylamine (0.84 ml) were

added to THF (20 ml). After the reaction mixture was stirred at room temperature for 20 hours, the reaction mixture was placed in water, and extraction was conducted using ethyl acetate-THF (1:1). The organic layer was 5 washed with water, saturated sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting crude crystals were recrystallized from ethyl acetate-hexane to give the titled compound (659 mg).

10 Melting point: 189 - 190°C

Reference Example 44

4-Anilinocarbonylbenzoic acid

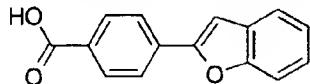


15 8 mol of aqueous sodium hydroxide solution (8 ml) was added to methanol (16 ml) - THF (6 ml) solution of 4-methyl anilinocarbonylbenzoate (511 mg), which was stirred at room temperature for 1 hour. 1 mol of hydrochloric acid was added to the reaction mixture to make the pH of the mixture 20 to 5, extraction was conducted using ethyl acetate-THF (1:1). The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting residue was washed with hexane to give the titled compound (480 mg).

25 Melting point: 305 - 307°C.

Reference Example 45

4-(2-Benzofuranyl)benzoic acid



30 Benzofuranyl-2-boric acid (2.1 g), palladium tetratriphenylphosphine (200 mg) and 2M aqueous sodium

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carbonate solution were added to toluene (40 ml) - ethanol (10 ml) solution of ethyl 4-bromobenzoate (2.3 g), which was refluxed at 80°C for 5 hours under an argon atmosphere.

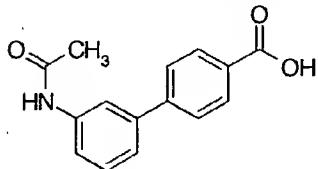
The reaction mixture was diluted with water, and

5 extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting residue was purified using silica gel chromatography (development solvent; ethyl acetate:hexane 10 = 1:4), and concentrated, which was dissolved in methanol (10 ml) - THF (10 ml). 8 mol of aqueous sodium hydroxide solution (8 ml) was added to the resulting solution at room temperature, which was stirred for 2 hours. After 1 mol of hydrochloric acid was added to the reaction mixture to 15 make the mixture acidic, extraction was conducted using ethyl acetate-THF (1:1). The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting residue was washed with hexane to give the titled compound (2.272 g).

20 Melting point: 292 - 294°C.

#### Reference Example 46

##### 3'-Acetylaminobiphenylcarboxylic acid

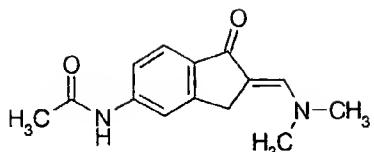


25 The titled compound was produced in the same manner as in Reference Example 45.

Melting point: 300 - 301°C

#### Reference Example 47

30 N-[2-[(E)-(Dimethylamino)methylidene]-1-oxo-2,3-dihydro-1H-inden-5-yl]acetamide

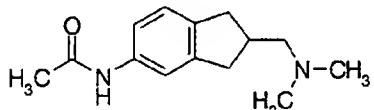


Dimethylformamide dimethylacetal was added to 5-acetamido-1-indanone (2.5 g, 13.2 mmol), which was stirred at 100°C for 3.5 hours, and cooled to room temperature. The precipitated crude products were collected, which was washed with ethyl acetate to give the titled compound (2.73 g).

10 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 2.08 (3H, s), 3.13 (6H, s), 3.87 (2H, s), 7.31 (1H, s), 7.52 (2H, m), 7.86 (1H, s), 10.16 (1H, s).

Reference Example 48

N-[2-[(Dimethylamino)methyl]-2,3-dihydro-1H-inden-5-yl] acetamide



15 N-[2-[(E)-(dimethylamino)methylidene]-1-oxo-2,3-dihydro-1H-inden-5-yl]acetamide (2.70 g, 12.3 mmol) obtained in Reference Example 47 and 10% palladium-carbon (0.3 g) were added to a mixed solution of methanol (60 ml) and acetic acid (6 ml), which was stirred at 40°C under a hydrogen atmosphere for 1 day. After the catalyst was filtered, the filtrate was distilled out under reduced pressure. 1N hydrochloric acid (15 ml) was added to the reaction mixture, which was washed with ethyl acetate.

20 Then, potassium carbonate was added to the mixture, and extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried using anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified using aluminum column chromatography (development solvent: ethyl acetate) to give the titled

25

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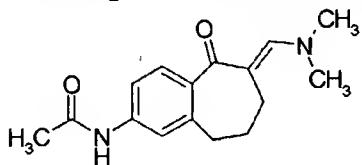
compound.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 2.15 (3H, s), 2.25 (6H, s), 2.28 (2H, m), 2.61 (3H, m), 3.02 (2H, m), 7.11 (2H, m), 7.26 (1H, s), 7.39 (1H, s).

5

Reference Example 49

N-[6-[(E)-(Dimethylamino)methylidene]-5-oxo-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-yl]acetamide



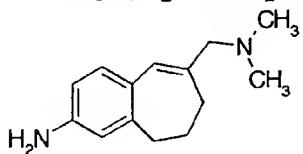
10 The titled compound was obtained by carrying out the same operation as in Reference Example 47, using N-(5-oxo-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-yl)acetamide.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.78-1.90 (2H, m), 2.17 (3H, s), 2.34 (2H, t, J = 6.6 Hz), 2.74 (2H, t, J = 6.8 Hz), 3.11 (6H, s), 7.21 (1H, d, J = 8.1 Hz), 7.48-7.63 (3H, m), 7.73 (1H, s).

Melting point: 177 - 180° C (crystallization solvent: ethyl acetate-diethyl ether)

20 Reference Example 50

8-[(Dimethylamino)methyl]-6,7-dihydro-5H-benzo[a]cyclohepten-3-amine



25 The titled compound was obtained as an oily substance by carrying out the same operation as in Example 41-2), using N-[6-[(E)-(dimethylamino)methylidene]-5-oxo-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-yl]acetamide obtained in Reference Example 49.

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.90-2.01 (2H, m), 2.22 (6H, s), 2.35 (2H, t, J = 6.3 Hz), 2.72 (2H, t, J = 5.4 Hz), 2.91 (2H, s), 3.7

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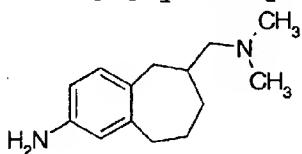
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(2H, br, NH<sub>2</sub>), 6.28 (1H, s), 6.40-6.50 (2H, m), 6.94 (1H, d, J = 7.8 Hz).

## Reference Example 51

5 6-[(Dimethylamino)methyl]-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-amine



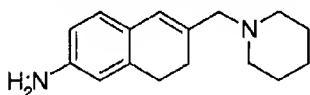
The titled compound was obtained as an oily substance, by carrying out the same operation as in Reference Example 10 48, using 8-[(dimethylamino)methyl]-6,7-dihydro-5H-benzo[a]cyclohepten-3-amine.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.30-1.63 (3H, m), 1.65-2.22 (10H, m), 2.44-2.80 (4H, m), 3.5 (2H, br, NH<sub>2</sub>), 6.35-6.48 (2H, m), 6.92 (1H, d, J = 7.8 Hz).

15

## Reference Example 52

6-(1-Piperidinylmethyl)-7,8-dihydro-2-naphthalenamine



1) A mixture of 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone (11 g) obtained in Example 41-1) and piperidine (100 ml) was refluxed with heating for 24 hours. After excess piperidine was distilled out under reduced pressure, the resulting residue was crystallized using tetrahydrofuran-isopropyl ether to give 6-acetamido-2-(1-piperidinylmethylidene)-1-tetralone (7 g) as a light yellow powder.

2) The titled compound was obtained as an amorphous powder by carrying out the same operations as in Example 41-2), using 6-acetamido-2-(1-piperidinylmethylidene)-1-tetralone obtained in above 1).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 1.44-1.57 (6H, m), 2.25-2.34 (6H, m), 2.72 (2H, t, J=8.0 Hz), 2.98 (2H, s), 3.59 (2H, s), 6.23 (1H,

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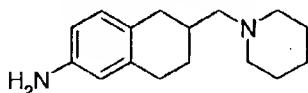
120

s), 6.45-6.47 (2H, m), 6.81 (1H, d, J=8.7 Hz).

Reference Example 53

6-(1-Piperidinylmethyl)-5,6,7,8-tetrahydro-2-

5 naphthalenamine

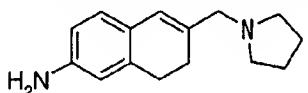


The titled compound was obtained as an amorphous powder by carrying out the same operations as in Reference Example 48, using 6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 52.

10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.25-2.82 (19H, m), 3.36 (2H, bs),  
6.44-6.49 (2H, m), 6.88 (1H, d, J=8.1 Hz).

Reference Example 54

15 6-(1-Pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine

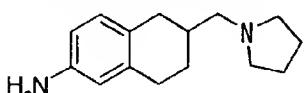


The titled compound was obtained as an amorphous powder by carrying out the same operations as in Reference Example 52, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone obtained in Example 41-1).

20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.76-1.80 (4H, m), 2.30 (2H, t, J = 7.8 Hz), 2.47-2.49 (4H, m), 2.74 (2H, t, J = 7.8 Hz), 3.13 (2H, s), 3.59 (2H, brs), 6.26 (1H, s), 6.45-6.47 (2H, m),  
25 6.82 (1H, d, J = 8.6Hz).

Reference Example 55

30 6-(1-Pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine



30 The titled compound was obtained as an amorphous

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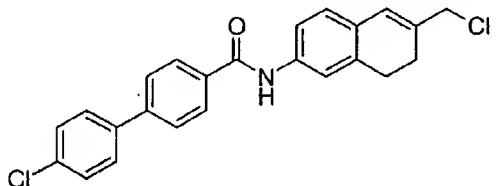
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powder by carrying out the same operations as in Reference Example 48, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

5       $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.45-1.90 (1H, m), 1.55-2.80 (16H, m),  
3.48 (2H, brs), 6.44 (1H, s), 6.47 (2H, d,  $J$  = 8.1 Hz),  
6.88 (2H, d,  $J$  = 8.1 Hz).

Reference Example 56

10      4'-Chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl] [1,1'-biphenyl]-4-carboxamide

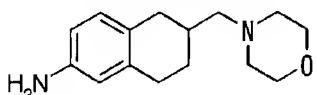


After 1-chloroethyl chloroformate (0.23 ml) was added to tetrahydrofuran solution (30 ml) of 4'-chloro-N-[6-(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide (750 mg) at -78°C, the temperature of the solution was raised to room temperature over 30 minutes. The solvent was distilled out under reduced pressure. The resulting residue was crystallized using tetrahydrofuran-n-hexane to give the 15 titled compound (600 mg).

20      Melting point: 179 - 181°C (crystallization solvent:  
tetrahydrofuran-n-hexane)

Reference Example 57

25      6-(4-Morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine



The titled compound was obtained as an amorphous powder by carrying out, in order, the same operations as 30 in Reference Example 52 and Reference Example 48, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-

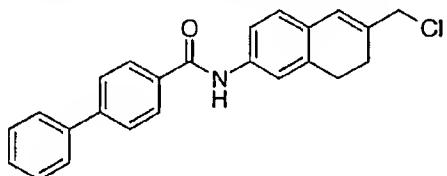
tetralone obtained in Example 41-1).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.22-1.41 (1H, m), 1.80-1.82 (2H, m), 2.22-2.34 (10H, m), 3.50 (2H, s), 3.69-3.72 (1H, m), 6.40 (1H, s), 6.44 (1H, d,  $J$  = 8.1 Hz), 6.85 (1H, d,  $J$  = 8.1 Hz).

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**Reference Example 58**

N-[6-(Chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

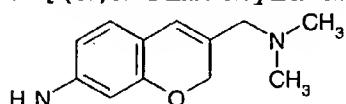


10 The titled compound was obtained by carrying out the same operations as in Reference Example 56, using N-[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Example 47.

15 Melting point: 163 - 165°C (crystallization solvent: tetrahydofuran-n-hexane)

**Reference Example 59**

3-[(N,N-Dimethylamino)methyl]-2H-chromen-7-amine



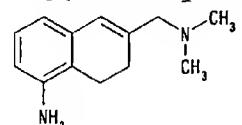
20

The titled compound was obtained by carrying out, in order, the same operations as in Examples 41-1) and 41-2), using 7-acetylamo-3,4-dihydrochromen-4-on.

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.20 (6H, s), 2.94 (2H, s), 3.66 (2H, brs), 4.71 (2H, s), 6.16-6.21 (2H, m), 6.76 (1H, d,  $J$  = 7.8 Hz).

**Reference Example 60**

6-[(Dimethylamino)methyl]-7,8-dihydro-1-naphthalenamine



1) Methyl 4-(2-aminophenyl)butanoate hydrochloride (7.20 g, 0.037 mol) synthesized by a known method by documents (*Synthetic communications*, 26(18), 3443 (1996)) and triethylamine (5.06 g, 0.05 mol) were dissolved in 5 tetrahydrofuran (60ml). Acetyl chloride (3.51 g, 0.045 mol) was added dropwise to the mixture, which was stirred at room temperature for 30 minutes. Ethyl acetate and 1N hydrochloric acid were added to the reaction mixture, and extraction was conducted. The organic layer was washed 10 with water, concentrated and dried. A mixed solution of ethyl acetate - n-hexane (1 : 1) was added to the residue. The crystallized product was collected by filtration, to give methyl 4-(2-acetylaminophenyl)butanoate (6.40g) as a white powder.

15  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.77-1.86 (2H, m), 2.29 (3H, s), 2.41-2.45 (2H, m), 2.59-2.62 (2H, m), 3.74 (3H, s), 7.03 (1H, t,  $J=7.3$  Hz), 7.11-7.12 (1H, m), 7.22 (1H, t,  $J=7.3$  Hz), 8.08 (1H, d,  $J=8.1$  Hz), 8.33 (1H, s).

20 2) Polyphosphoric acid (100g) was heated at  $130^\circ\text{C}$ , then methyl 4-(2-acetylaminophenyl)butanoate (6.40g, 0.027mol) obtained in 1) was added under stirring. After stirring for 1 hour, the reaction mixture was poured into ice water, and ethyl acetate and water were added, then extraction was conducted by adding water. The organic 25 layer was washed with saturated sodium hydrogen carbonate solution and aqueous sodium chloride solution, and concentrated. A mixed solution of ethyl acetate - n-hexane (1:1) was added to the residue, and the crystallized product was collected by filtration, to give 5-acetylamino-1-tetralone (2.80g) as a white powder.

30  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 2.10-2.19 (2H, m), 2.24 (3H, s), 2.66 (2H, t,  $J=6.3$  Hz), 2.84 (2H, t,  $J=5.7$  Hz), 7.06 (1H, brs), 7.34 (1H, t,  $J=7.5$  Hz), 7.82 (1H, d,  $J=7.5$  Hz), 7.95 (1H, d,  $J=7.5$  Hz).

35 3) 5-Acetylamino-1-tetralone (0.6g, 3.0 mmol) obtained was dissolved in dimethylformamide dimethylacetal

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(20ml), which was refluxed with heating for 4 hours. The crystallized product was collected by filtration, which was washed with ethyl acetate, to give 5-acetylamino-2-(dimethylamino)methylidene-1-tetralone (0.58g) as a 5 yellow powder.

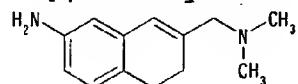
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.21 (3H, s), 2.68-2.72 (2H, m), 2.86-2.90 (2H, m), 3.11 (6H, s), 7.26-7.31 (2H, m), 7.62 (1H, m), 7.69 (1H, s), 7.92 (1H, m).

4) Sodium triacetoxyhydroborate (424 mg, 2.0 mmol) 10 was dissolved in a mixed solution of ethyl acetate (5ml) and tetrahydrofuran (1ml) under ice-cooling. 5-Acetylamino-2-dimethylaminomethylidene-1-tetralone (129 mg, 0.5 mmol) obtained in 3) was added to the mixture, which was stirred for 15 minutes. The reaction mixture was 15 concentrated, and methanol (10ml) was added to the residue, and sodium borohydride (38 mg, 1 mmol) was added under ice-cooling. After stirring for 1 hour, the reaction mixture was concentrated. 5N Hydrochloric acid and ethyl acetate were added to the residue, and extraction was 20 conducted. The water layer was refluxed with heating for 2 hours. 4N sodium hydroxide solution and ethyl acetate were added to the reaction mixture, and extraction was conducted. The organic layer was washed with water, and concentrated. The residue was purified by alumina column 25 chromatography (development solvent; ethyl acetate : n-hexane=1:1), to give the titled compound (80 mg) as a colorless oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.24(6H, s), 2.37(2H, t, J=8.1 Hz), 2.63(2H, t, J=8.1 Hz), 2.97(2H, s), 3.58(2H, brs), 6.29(1H, s,), 6.53(1H, d, J=8.1 Hz), 6.57 (1H, d, J=8.1 Hz), 30 6.97(1H, t, J=8.1 Hz).

#### Reference Example 61

7-[(Dimethylamino)methyl]-5,6-dihydro-2-naphthalenamine



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1) 7-Nitro-1-tetralone (8.32 g, 0.044 mol) and concentrated hydrochloric acid (24 ml, 0.29 mol) were dissolved in methanol (100 ml), and an iron powder (7.30 g, 0.13 mol) was gradually added over 1 hour. After 5 stirring for 1 hour, the reaction mixture was concentrated.

4N Sodium hydroxide solution and ethyl acetate were added to the residue, and extraction was conducted. The organic layer was dried, and concentrated. Tetrahydrofuran (100 ml) and triethylamine (5.05 g, 0.05 mol) was added to the 10 residue. Further, acetyl chloride (3.92 g, 0.05 mol) was added under ice-cooling. After stirring for 30 minutes, ethyl acetate and 1N hydrochloric acid were added, and extraction was conducted. The organic layer was concentrated, and the residue was purified with silica gel 15 column chromatography (development solvent: ethyl acetate), to give 7-acetylamino-1-tetralone (7.52 g) as a white powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.09-2.18 (2H, m), 2.21(3H, s), 2.65 (2H, t, J=6.3 Hz), 2.94 (2H, t, J=6.3 Hz), 7.24 (1H, d, J=8.4 Hz), 7.82 (1H, s), 7.98 (1H, brs), 8.15 (1H, d, J=7.5 Hz).

2) 7-Acetylamino-2-[(dimethylamino)methylidene]-1-tetralone (2.95 g) was obtained as a white powder by the same method as in Reference Example 60-3), using 7-acetylamino-1-tetralone (3.00 g, 0.0148 mol) obtained in 25 1).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.17 (3H, s), 2.78-2.82 (2H, m), 2.88-2.93 (2H, m), 3.14 (6H, s), 7.14 (1H, d, J=8.1 Hz), 7.74 (1H, s), 7.76 (1H, s), 8.09-8.12 (1H, m), 8.24 (1H, s).

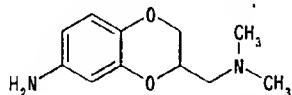
3) The titled compound (300 mg) was obtained as a 30 colorless oily substance by the same method as in Reference Example 60-4), using 7-acetylamino-2-[(dimethylamino)methylidene]-1-tetralone (628 mg, 2.43 mmol) obtained in 2).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.23 (6H, s); 2.29 (2H, t, J=8.4 Hz), 2.71 (2H, t, J=8.4 Hz), 2.97 (2H, s), 3.52 (2H, brs), 6.24 (1H, s,), 6.41 (1H, s,), 6.46 (1H, d, J=7.8 Hz), 6.90 (1H, d,

J=7.8 Hz).

Reference Example 62

N,N-Dimethyl-N-[(7-amino-2,3-dihydro-1,4-benzodioxin-2-  
5 yl)methyl]amine



10 1) 1,2-Dihydroxy-4-nitrobenzene (5.00 g, 0.032 mol), potassium carbonate (9.67 g, 0.07 mol) and epibromohydrin (5.30 g, 0.039 mol) were dissolved in dimethylformamide (100ml), which was stirred at 100°C for 1 hour. Water was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water, and concentrated. The residue was purified by alumina column chromatography (development solvent : ethyl acetate). The eluent was washed with a mixed solution of ethyl acetate - n-hexane (1:1), to give (7-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (3.31 g) as a white powder.

15 20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.95-1.99 (1H, m), 3.89-3.97 (2H, m), 4.19-4.29 (2H, m), 4.41-4.45 (1H, m), 6.96 (1H, d, J=8.6 Hz), 7.78-7.81 (2H, m).

25 30 35 2) (7-Nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (1.00 g, 4.74 mmol) obtained in 1) and triethylamine (719 mg, 7.10 mmol) were dissolved in dimethylformamide (30 ml), and methanesulfonyl chloride (651 mg, 5.68 mmol) was added, which was stirred at room temperature for 30 minutes. Then, an aqueous dimethylamine solution was added and stirred at 60°C for 5 hours. Water was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water, and concentrated. The residue was purified by alumina column chromatography (development solvent : ethyl acetate : n-hexane = 3:7), to give N,N-dimethyl-N-[(7-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine (802 mg) as a colorless oily substance.

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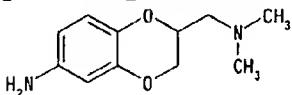
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.34 (6H, s), 2.50-2.68 (2H, m), 4.02-4.09 (2H, m), 4.30-4.36 (1H, m), 4.39-4.44 (2H, m), 6.94 (1H, d, J=8.9Hz), 7.76-7.84 (2H, m).

3) N,N-Dimethyl-N-[(7-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine (802 mg, 3.37 mmol) obtained in 2) and concentrated hydrochloric acid (3 ml) was dissolved in methanol (10 ml), and an iron powder (0.80 g, 14 mmol) was quietly added over 1 hour. After stirring for 1 hour, the reaction mixture was concentrated. 4N Sodium hydroxide solution and ethyl acetate were added to the residue, and extraction was conducted. The organic layer was dried, and concentrated. The residue was purified by silica gel column chromatography (development solvent: ethyl acetate - n-hexane = 3:7), to give the titled compound (514 mg) as a colorless oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.32 (6H, s), 2.43-2.64 (2H, m), 3.40 (2H, s), 3.86-3.93 (1H, m), 4.19-4.27 (2H, m), 6.18-6.22 (1H, m), 6.29 (1H, s), 6.67 (1H, d, J=8.7 Hz).

20 Reference Example 63

N,N-Dimethyl-N-[(6-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine



1) 1,2-Dihydroxy-4-nitrobenzene (4.65 g, 0.030 mol), potassium carbonate (8.71 g, 0.063 mol) and methoxymethyl chloride (2.42 g, 0.030 mol) were dissolved in dimethylformamide (50 ml), which was stirred at 40°C for 30 minutes. Epibromohydrin (7.20 g, 0.045 mol) was added to the mixture, which was stirred at 60°C for 80 minutes. Then water was added, and extraction was conducted using ethyl acetate. The organic layer was washed with water, and concentrated. The residue was purified by alumina column chromatography (development solvent: ethyl acetate - n-hexane = 1:4), to give 2-[(2-(methoxymethoxy)-5-nitrophenoxy)methyl]oxirane (2.61 g) as a white powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.79-2.81 (1H, m), 2.93-2.96 (1H, m), 3.41 (1H, m), 3.53 (3H, s), 4.01-4.07 (1H, m), 4.40-4.45 (1H, m), 5.32 (2H, s), 7.22 (1H, d, J=9.0 Hz), 7.82-7.91 (2H, m).

5        2) 2-[(2-(Methoxymethoxy)-5-nitrophenoxy)methyl]oxirane (4.00 g, 0.016 mol) obtained in 1) was dissolved in methanol (50 ml), and 10% hydrochloric acid-methanol solution (10 ml) was added, which was stirred at room temperature for 30 minutes. The 10 solvent was concentrated, and methanol (30 ml) and potassium carbonate (6.50 g, 0.047 mol) were added to the residue, which was stirred at 60°C for 1 hour. The solvent was concentrated, water was added, and extraction was conducted using ethyl acetate. The organic layer was 15 washed with water, and concentrated. The residue was purified by alumina column chromatography (development solvent: ethyl acetate), to give (6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (2.12 g) as a white powder.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.90-1.94 (1H, m), 3.89-3.97 (2H, m), 20 4.19-4.28 (2H, m), 4.41-4.45 (1H, m), 6.97 (1H, d, J=8.6 Hz), 7.78-7.82 (2H, m).

25        3) N,N-Dimethyl-N-[(6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine (910 mg) was obtained as a colorless oily substance, by the same method as in Reference Example 62-2), using (6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (1.00 g, 4.74 mmol) obtained in 2).

30        <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.35 (6H, s), 2.52-2.70 (2H, m), 3.98-4.05 (2H, m), 4.35-4.39 (3H, m), 6.95-6.98 (1H, m), 7.77-7.80 (2H, m).

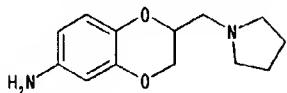
35        4) The titled compound (750 mg) was obtained as a colorless oily substance, by the same method as in Reference Example 62-3), using N,N-dimethyl-N-[(6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine (910 mg, 3.82 mmol) obtained in 3).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.32 (6H, s), 2.43-2.64 (2H, m), 3.40 (2H,

s), 3.86-3.92 (1H, m), 4.13-4.27 (2H, m), 6.19-6.28 (2H, m), 6.67-6.70 (1H, m).

Reference Example 64

- 5 1-[(6-Amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]pyrrolidine

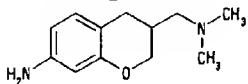


10 1) 1-[(6-Nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]pyrrolidine (1.30 g) was obtained as a colorless oily substance, by the same method as in Reference Example 62-2), using (6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (1.12 g, 5.30 mmol) and pyrrolidine (10 ml).  
15  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.79-1.83 (4H, m), 2.60-2.62 (4H, m), 2.78 (2H, d,  $J=5.9$  Hz), 4.00-4.07 (1H, m), 4.38-4.42 (2H, m), 6.95-6.98 (1H, m), 7.76-7.80 (2H, m).

20 2) The titled compound (1.03 g) was obtained as a colorless oily substance, by the same method as in Reference Example 62-3), using 1-[(6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]pyrrolidine (1.30 g, 4.92 mmol).  
 $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.74-1.83 (4H, m), 2.54-2.63 (4H, m), 2.69-2.72 (2H, m), 3.40 (2H, s), 3.91-3.97 (1H, m), 4.18-4.30 (2H, m), 6.18-6.25 (2H, m), 6.70 (1H, d,  $J=8.4$  Hz).

- 25 Reference Example 65

N-[(7-Amino-3,4-dihydro-2H-chromen-3-yl)methyl]-N,N-dimethylamine



30 3-[(N,N-Dimethylamino)methyl]-2H-chromen-7-amine (150 mg, 0.73 mmol) obtained in Reference Example 59, 1N hydrochloric acid (0.5 ml) and 10% palladium carbon (40 mg) was dissolved in methanol (5 ml), and catalytic hydrogenation was conducted under normal temperature and normal pressure. After a catalyst was filtered out, the

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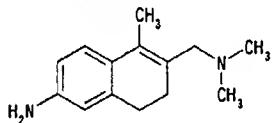
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filtrate was concentrated, and the residue was purified by alumina column chromatography (development solvent; ethyl acetate : n-hexane = 3:7), to give the titled compound (15 mg) as a colorless oily substance.

5      $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 2.20-2.24 (3H, m), 2.24(6H, m), 2.30-2.40 (1H, m), 2.75-2.80 (1H, m), 3.60 (1H, m), 3.75-3.80 (2H, m), 4.20-4.25 (1H, m), 6.20 (1H, m), 6.21-6.25 (1H, m), 6.82 (1H, d,  $J=7.8$  Hz).

10    Reference Example 66

6-[(Dimethylamino)methyl]-5-methyl-7,8-dihydro-2-naphthalenamine



15    1) 6-Acetylmino-1-tetralone (5.5 g, 0.027 mol) and dimethylmethylenammonium chloride (6.3 g, 0.068 mol) were dissolved in a mixed solution of acetonitrile (100 ml) and tetrahydrofuran (100 ml), which was stirred for 48 hours.

16    The crystallized product was collected by filtration, washed with tetrahydrofuran, and dissolved in ethyl acetate. 0.5N Sodium hydroxide solution was added to the solution for liquid separation. The organic layer was concentrated, to give 6-acetylmino-2-[(dimethylamino)methyl]-1-tetralone (4.48 g) as a colorless oily substance.

20    2) 6-Acetylmino-2-[(dimethylamino)methyl]-1-tetralone (260 mg, 1.00 mmol) obtained was dissolved in tetrahydrofuran (10 ml). 1M Methyl magnesium bromide - tetrahydrofuran solution (3 ml)(3.00 mmol) was added to the solution under ice-cooling, which was stirred at room

25    temperature for 16 hours. Aqueous ammonium chloride solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was concentrated, and 5N hydrochloric acid and ethyl acetate were added to the residue for liquid separation.

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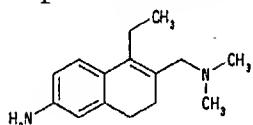
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Concentrated hydrochloric acid was added to the water layer, which was refluxed for 4 hours. The reaction mixture was concentrated, and 1N sodium hydroxide solution and ethyl acetate were added to the residue and extraction was 5 conducted. The organic layer was concentrated, and the residue was purified by alumina column chromatography (development solvent; ethyl acetate : n-hexane = 3:7), to give the titled compound (83 mg) as a colorless oily substance.

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 2.04 (3H, s), 2.24 (6H, s), 2.28 (2H, t,  $J=7.4$  Hz), 2.66 (2H, t,  $J=7.4$  Hz), 3.04 (2H, s), 3.62 (2H, s), 6.49 (1H, s), 6.51-6.55 (1H, m), 7.10 (1H, d,  $J=8.1$  Hz).

15 Reference Example 67

6-[(Dimethylamino)methyl]-5-ethyl-7,8-dihydro-2-naphthalenamine

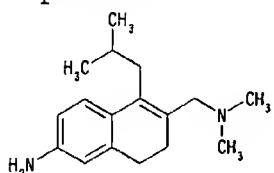


20 The titled compound was obtained as a colorless oily substance by the same manner as in Reference Example 66-2), using 6-acetylmino-2-(dimethylamino)methyl-1-tetralone obtained in Reference Example 66-1) and ethyl magnesium bromide.

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.06 (3H, t,  $J=7.5$  Hz), 2.24 (6H, s), 2.27 (2H, m), 2.52-2.66 (4H, m), 3.04 (2H, s), 3.61 (2H, s), 6.51 (1H, s), 6.51-6.55 (1H, m), 7.11 (1H, d,  $J=8.1$  Hz).

Reference Example 68

30 6-[(Dimethylamino)methyl]-5-isobutyl-7,8-dihydro-2-naphthalenamine



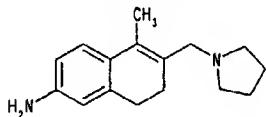
The titled compound was obtained as a colorless oily substance by the same manner as in Reference Example 66-2), using 6-acetylamino-2-[(dimethylamino)methyl]-1-tetralone obtained in Reference Example 66-1) and isobutyl 5 magnesium bromide.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.88 (6H, d, J=6.7 Hz), 1.73-1.79 (1H, m), 2.21 (6H, s), 2.28 (2H, t, J=7.0 Hz), 2.44 (2H, d, J=7.3 Hz), 2.63 (2H, t, J=7.0 Hz), 3.09 (2H, s), 3.60 (2H, s), 6.49 (1H, s), 6.51-6.53 (1H, m), 7.08 (1H, d, J=7.8 Hz).

10

## Reference Example 69

5-Methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine



15

1) 6-Acetylamino-2-[(dimethylamino)methylidene]-1-tetralone (4.90 g, 0.017 mol) obtained in Example 41-1) was suspended in pyrrolidine (25 ml), which was refluxed with heating for 2 hours. The crystallized product was collected by filtration, washed with a mixed solution of ethyl acetate and n-hexane (1:1), to give 6-acetylamino-2-(1-pyrrolidinylmethylidene)-1-tetralone (5.03 g) as yellow crystals.

20

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.75-2.00 (4H, m), 2.19 (3H, s), 2.70-3.00 (4H, m), 3.50-3.70 (4H, m), 7.20-7.25 (1H, m), 7.67 (1H, s), 7.70-7.90 (2H, m), 7.97 (1H, d, J=8.4 Hz).

25

2) Sodium triacetoxyhydroborate (3.18 g, 0.015 mol) was dissolved in a mixed solution of ethyl acetate (50 ml) and tetrahydrofuran (12.5 ml) under ice-cooling, and 6-acetylamino-2-(1-pyrrolidinylmethylidene)-1-tetralone (2.84 g, 0.01mol) obtained in 1) was added. After stirring for 1 hour, the reaction mixture was concentrated.

1N Sodium hydroxide solution and ethyl acetate were added to the residue, which was stirred. The crystallized product was collected by filtration, washed with a mixed solution

30

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of ethyl acetate and n-hexane (1:1), to give 6-acetylamino-2-(1-pyrrolidinylmethyl)-1-tetralone (2.65 g) as a white powder.

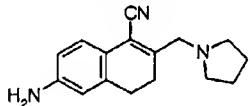
5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.78 (4H, m), 1.90-2.02 (1H, m), 2.20 (3H, s), 2.35-2.98 (10H, m), 7.20-7.23 (1H, m), 7.57 (1H, s), 7.66 (1H, m), 7.97 (1H, d,  $J=8.4$  Hz).

3) The titled compound was obtained by the same manner as in Reference Example 66-2), using 6-acetylamino-2-(1-pyrrolidinylmethyl)-1-tetralone obtained in 2).

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.73-1.79 (4H, m), 2.04 (3H, s), 2.31 (2H, t,  $J=7.4$  Hz), 2.49-2.54 (4H, m), 2.65 (2H, t,  $J=7.8$  Hz), 3.24 (2H, s), 3.60 (2H, brs), 6.48-6.54 (2H, m), 7.09 (1H, d,  $J=8.1$  Hz).

15 Reference Example 70

6-Amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-1-naphthalenecarbonitrile



Trimethylsilylnitrile (1.02 ml, 7.68 mmol) and zinc iodide (22 mg, 0.0698 mmol) were added to dichloroethane solution (9 ml) of 6-acetylamino-2-(1-pyrrolidinylmethyl)-1-tetralone (1.00 g, 3.49 mmol) obtained in Reference Example 69-2), which was stirred at room temperature for 2 days. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the obtained oily substance, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified by alumina column chromatography (development solvent; ethyl acetate), to give trimethylsilylcyanohydrin form (1.21 g) as an oily substance. 2.5N Hydrochloric acid was added to the oily substance (978 mg, 2.73 mmol), which was stirred at 100°C for 1.5 hours. The aqueous solution obtained was

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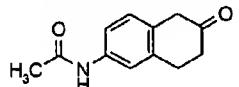
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washed with ethyl acetate. Potassium carbonate was added to the water layer to make it alkaline, and extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried over 5 anhydrous sodium sulfate, and the solvent was distilled out under reduced pressure. The resulting oily substance was purified by alumina column chromatography (development solvent; hexane:ethyl acetate = 5:1), to give the titled compound (358 mg).

10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.80 (4H, m), 2.56 (6H, m), 3.73 (2H, m), 3.50 (2H, s), 3.77 (2H, br), 6.46 (1H, s), 6.55 (1H, d,  $J$  = 8.1 Hz), 7.26 (1H, d,  $J$  = 8.1 Hz).

## Reference Example 71

## 15 6-Acetamido-2-tetralone



1) Sodium borohydride (931 mg, 24.6 mmol) was added to a methanol solution (60 ml) of 6-acetamido-1-tetralone (5.00 g, 24.6 mmol) under ice-cooling, which was stirred 20 at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then, the solvent was distilled out under reduced pressure. p-Toluenesulfonic acid (468 mg, 2.46 mmol) and toluene (120 ml) were added to the obtained alcohol form (5.05 g, 24.6 mmol), which was stirred at 100 °C for 1 hour. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with saturated aqueous sodium chloride solution, 25 dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent; hexane:ethyl acetate = 1:1), and powdered with hexane to give N-(7,8-dihydro-2-naphthalenyl)acetamide (3.17 g).

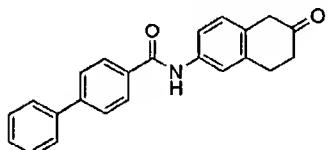
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 2.16 (3H, s), 2.29 (2H, m), 2.28 (2H, m), 5.97 (1H, m), 6.42 (2H, d, J=9.6 Hz), 6.97 (1H, d, J=8.1 Hz), 7.14 (1H, br), 7.20 (1H, m), 7.32 (1H, s).

2) m-Chloroperbenzoic acid (5.13 g, 20.8 mmol) was 5 added to a chloroform solution (80 ml) of N-(7,8-dihydro-2-naphthalenyl)acetamide (3.00 g, 16.0 mmol) obtained in 1) under ice-cooling, which was stirred at room temperature for 2 hours. Ethyl acetate was added to the reaction mixture, which was washed with saturated sodium 10 hydrogencarbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by alumina B column chromatography (development solvent; hexane:ethyl 15 acetate = 1:1). 1N Sodium hydroxide solution (10.7 ml) was added to a methanol solution (100 ml) of the obtained oily substance (3.20 g, 8.89 mmol) under ice-cooling, which was stirred at room temperature for 30 minutes. The solvent was distilled out under reduced pressure. Ethyl acetate 20 was added to the residue, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by alumina B column chromatography (development 25 solvent; ethyl acetate:methanol = 10:1). p-Toluenesulfonic acid (50mg, 0.262 mmol) and toluene (26 ml) were added to the obtained diol (596 mg, 2.62 mmol), which was stirred at 120°C for 3 hours. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the 30 residue, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent; hexane:ethyl acetate = 1:3), and powdered with diisopropyl ether, to 35 give the titled compound (231 mg).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 2.18 (3H, s), 2.54 (2H, m), 3.04 (2H, m), 3.76 (2H, s), 7.06 (1H, d, J=8.1 Hz), 7.21 (1H, dd, J=8.1, 2.0 Hz), 7.31 (1H, br), 7.61 (1H, d, J=2.0 Hz).

## 5 Reference Example 72

N-(6-Oxo-5,6,7,8-tetrahydro-2-naphthalenyl)[1,1'-biphenyl]-4-carboxamide



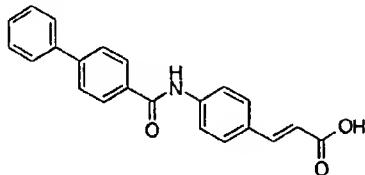
Concentrated hydrochloric acid (1.5 ml) was added to 10 6-acetamido-2-tetralone (20 mg, 0.098 mmol) obtained in Reference Example 71, which was stirred at 100°C for 1 hour, and the solvent was distilled out under reduced pressure.

Ethyl acetate was added to the residue, which was washed 15 with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. [1,1'-Biphenyl]-4-carbonyl chloride (21.3 mg, 0.098 mmol) was added to a dimethylformamide solution (0.5 ml) of the obtained oily substance and 20 triethylamine (0.014 ml, 0.098 mmol) under ice-cooling, which was stirred at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, which was washed with 1N hydrochloric acid, aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent 25 was distilled out under reduced pressure. The resulting residue was purified by silica gel column chromatography (development solvent; hexane:ethyl acetate = 1:1), to give the titled compound (10 mg).

30 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 2.56 (2H, t, J=6.6 Hz), 3.08 (2H, t, J=6.6 Hz), 3.57 (2H, s), 7.11 (1H, d, J=8.1 Hz), 7.43 (4H, m), 7.64 (2H, m), 7.72 (3H, m), 7.96 (3H, m).

## Reference Example 73

(E)-3-[4-[(1,1'-biphenyl)-4-ylcarbonyl]amino]phenyl]-2-propenoic acid

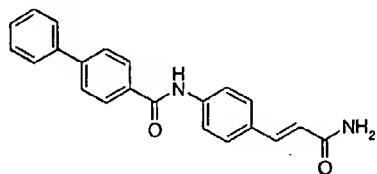


5       4-Phenylbenzoyl chloride (2.00 g, 9.23 mmol) was added to a mixed solution of 4-aminocinnamic acid (1.51 g, 9.23 mmol) and sodium hydrogen carbonate (2.33 g, 27.7 mmol) in water and diethyl ether under ice-cooling, which was stirred for 5 hours. After the reaction mixture was  
10      separated, 5N hydrochloric acid was added to water layer, and the precipitated crude product was washed with water and ethyl acetate, to give the titled compound (1.34 g).  
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 6.84 (1H, d, J = 16.0 Hz), 7.43-7.93 (12H, m), 8.09 (2H, d, J = 8.4 Hz), 10.51 (1H, s).

15

## Reference Example 74

N-[4-[(E)-3-Amino-3-oxo-1-propenyl]phenyl][1,1'-biphenyl]-4-carboxamide



20       Chloro isobutylcarbonate (0.453 ml, 3.49 mmol) was added to a dimethylformamide suspension of (E)-3-[4-[(1,1'-biphenyl)-4-ylcarbonyl]amino]phenyl]-2-propenoic acid (1.00 g, 2.91 mmol) obtained in Reference Example 73 and triethylamine (0.527 ml, 3.79 mmol) under  
25      ice-cooling, which was stirred for 30 minute. The solvent was distilled out under reduced pressure. Sodium hydrogencarbonate solution was added to the residue, and the precipitated crude product was washed with water and acetonitrile, to give the titled compound (936 mg).

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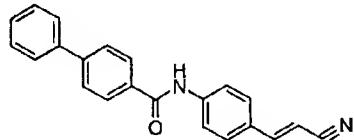
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<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ : 6.56 (1H, d, J = 15.6 Hz), 7.05 (1H, br), 7.52 (7H, m), 7.86 (6H, m), 8.08 (2H, d, J = 7.6 Hz).

Reference Example 75

- 5 N-[4-[(E)-2-Cyanoethenyl]phenyl][1,1'-biphenyl]-4-carboxamide

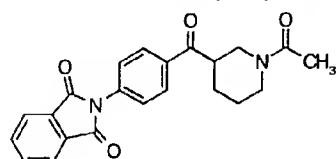


Cyanuric chloride (727 mg, 3.94 mmol) was added to a dimethylformamide suspension of (E)-3-[4-[(1,1'-biphenyl)-4-ylcarbonyl]amino]phenyl]-2-propenic acid (900 mg, 2.63 mmol) obtained in Reference Example 74 at room temperature, which was stirred for 1 hour. After the solvent was distilled out under reduced pressure, the residue was dissolved in chloroform, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was stillled out under reduced pressure. The resulting residue was purified by silica gel column chromatography (development solvent : chloroform : ethyl acetate = 20:1), to give the titled compound (561 mg) as a colorless powder from diethyl ether.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ : 6.37 (1H, d, J = 16.4 Hz), 7.43-7.51 (4H, m), 7.65-7.93 (8H, m), 8.08 (2H, d, J = 8.6 Hz).

- 25 Reference Example 76

2-[4-[(1-Acetyl-3-piperidinyl)carbonyl]phenyl]-1H-isoindol-1,3(2H)-dione



1) Thionyl chloride (2.12 ml, 32.1 mmol) was added to 30 fluorobenzene solution (20 ml) of 1-acetyl-3-

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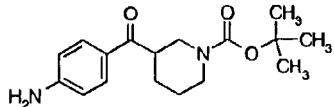
piperidinecarboxylic acid (5.00 g, 29.2 mmol) under ice-cooling, which was stirred at room temperature for 30 minutes. Aluminum chloride (9.74 g, 73.0 mmol) was added to the solution, which was stirred at 90°C for 1 hour. The 5 reaction mixture was poured in ice, and extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, saturated sodium hydrogencarbonate solution, and again saturated aqueous sodium chloride solution, dried over anhydrous 10 sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent ; hexane : ethyl acetate = 1:1), to give (1-acetyl-3-piperidinyl)(4-fluorophenyl)methanone (4.93 g). 15  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  : 1.61 (2H, m), 1.80 (2H, m), 2.11 and 2.15 (3H, s and s), 2.71 (1H, m), 3.11 and 3.42 (2H, m), 3.87 (1H, m), 4.53 and 4.83 (1H, m), 7.18 (2H, m), 8.02 (2H, m).

2) A dimethylformamide solution (50 ml) of (1-acetyl-3-piperidinyl)(4-fluorophenyl)methanone (4.92 g, 19.7 mmol) obtained in 1) and potassium phthalimide (3.66g, 19.7mmol) was stirred at 100°C for 12 hours under nitrogen atmosphere. The insoluble matters were filtered off, and the solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed 20 with 1N hydrochloric acid and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent ; ethyl 25 acetate), to give the titled compound (4.18 g) as a colorless powder from ethyl acetate - diisopropyl ether (1:5).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  : 1.66 (2H, m), 1.86 (2H, m), 2.13 and 2.15 (3H, s and s), 2.74 (1H, m), 3.11 and 3.43 (2H, m), 3.88 (1H, m), 4.54 and 4.85 (1H, m), 7.66 (2H, m), 7.82 (2H, m), 30 7.99 (2H, m), 8.10 (2H, m).

## Reference Example 77

## tert-Butyl 3-(4-aminobenzoyl)-1-piperidinecarboxylate



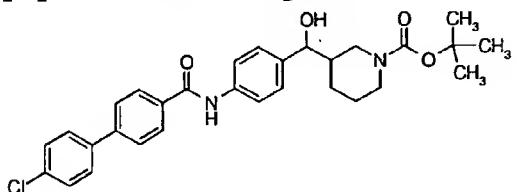
- 5        1) Concentrated hydrochloric acid (53 ml) was added to 2-[4-[(1-acetyl-3-piperidinyl)carbonyl]phenyl]-1H-isoindol-1,3(2H)-dione (4.00 g, 10.6 mmol) obtained in Reference Example 76, which was stirred at 100°C for 16 hours, and then insoluble matters were filtered off.
- 10      Potassium carbonate was added to the filtrate to make it alkaline, and extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure.
- 15      The resulting residue was powdered with diisopropyl ether, to give (4-aminophenyl)(3-piperidinyl)methanone (1.69 g).  
 $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  : 1.59-1.85 (4H, m), 2.68-2.72 (2H, m), 3.30 (2H, m), 3.45 (1H, m), 6.62 (2H, m), 7.74 (2H, m).
- 20      2) t-Butyl dicarbonate (0.562 ml, 2.45 mmol) was added to a tetrahydrofuran solution (12 ml) of (4-aminophenyl)(3-piperidinyl)methanone (500 mg, 2.45 mmol) obtained in 1) under ice-cooling, which was stirred for 1.5 hours. Ethyl acetate was added to the reaction mixture, which was washed with saturated sodium hydrogencarbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent; hexane:ethyl acetate = 1:1), to give the titled compound (831 mg).
- 25       $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.47 (9H, s), 1.47-1.52 (2H, m), 1.67-1.74 (2H, m), 2.00 (1H, m), 2.72 (1H, m), 2.90 (1H, m), 3.32 (1H, m), 4.13 (3H, m), 6.66 (2H, d,  $J=8.4\text{Hz}$ ), 7.84 (2H, d,  $J=8.4\text{Hz}$ ).

## Reference Example 78

tert-Butyl 3-[4-[(4'-chloro[1,1'-biphenyl]-4-

yl)carbonyl]amino]phenyl](hydroxy)methyl]-1-

5 piperidinecarboxylate



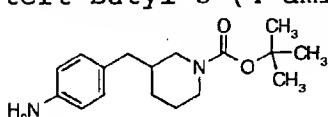
tert-Butyl 3-[4-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]benzoyl]-1-piperidinecarboxylate (506 mg, 0.975 mmol) obtained in Example 127-1) was dissolved

10 in a mixed solution of methanol and tetrahydrofuran (1:1) (10 ml). Sodium borohydride (73.8 mg, 1.95 mmol) was added to the solution under ice-cooling, which was stirred at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. Diisopropyl ether was added to the residue, to give the titled compound (488mg) as a colorless powder.

15 20 FABMS(pos) 521.2 [M+H]<sup>+</sup>

## Reference Example 79

tert-Butyl 3-(4-aminobenzyl)-1-piperidinecarboxylate



25 Sodium borohydride (433 mg; 11.5 mmol) was added to a methanol solution (25 ml) of tert-butyl 3-(4-aminobenzyl)-1-piperidinecarboxylate (1.74g, 5.73mmol) obtained in Reference Example 77 under ice-cooling, which was stirred at room temperature for 1 hour. Ethyl acetate 30 was added to the reaction mixture, which was washed with saturated aqueous sodium chloride solution, dried over

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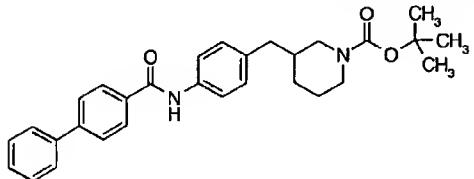
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anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by alumina Bcolumn chromatography (development solvent ; ethyl acetate), to give an alcohol form. 1N hydrochloric acid (9.79 ml) and 10% palladium carbon (200 mg) were added to a methanol solution (300 ml ) of the obtained alcohol form (1.00 g, 3.26 mmol), which was stirred for 16 hours under hydrogen atmosphere. The catalyst was filtered off, potassium carbonate was added to the filtrate to make it alkaline, and then the solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent ; hexane - ethyl acetate = 1:1), to give the titled compound (813 mg).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 1.46-1.76 (14H, m), 2.25-2.80 (2H, m), 3.14 (2H, m), 3.76 (4H, m), 6.64 (2H, m), 7.01 (2H, m).

#### Reference Example 80

tert-Butyl 3-[4-[(1,1'-biphenyl)-4-ylcarbonyl]amino]benzyl]-1-piperidinecarboxylate



25

The titled compound was obtained by carrying out the same operation as in Example 1, using tert-butyl 3-(4-aminobenzyl)-1-piperidinecarboxylate obtained in Reference Example 79 and [1,1'-biphenyl]-4-carboxylic acid.

Elemental analysis for C<sub>30</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub> · 0.5H<sub>2</sub>O

Calcd. : C, 75.13; H, 7.36; N, 5.84.

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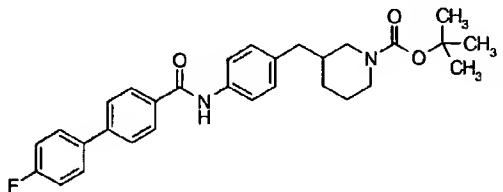
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Found : C, 74.83; H, 7.25; N, 5.65.

Melting point: 135 - 137°C

## Reference Example 81

- 5   tert-Butyl 3-[4-[(4'-fluoro[1,1'-biphenyl]-4-  
y1)carbonyl]amino]benzyl]-1-piperidinecarboxylate



The titled compound was obtained by carrying out the same operation as in Example 1, using tert-butyl 3-(4-  
10 aminobenzyl)-1-piperidinecarboxylate obtained in Reference Example 80 and 4'-fluoro[1,1'-biphenyl]-4-carboxylic acid.

Elemental analysis for  $C_{30}H_{33}FN_2O_3 \cdot 0.5H_2O$ 

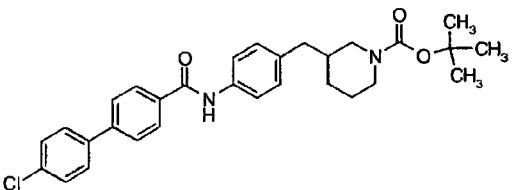
Calcd. : C, 72.41; H, 6.89; N, 5.63.

15   Found : C, 72.30; H, 7.07; N, 5.60.

Melting point: 138 - 141°C

## Reference Example 82

- 20   tert-Butyl 3-[4-[(4'-chloro[1,1'-biphenyl]-4-  
y1)carbonyl]amino]benzyl]-1-piperidinecarboxylate



The titled compound was obtained by carrying out the same operation as in Example 1, using tert-butyl 3-(4-  
25 aminobenzyl)-1-piperidinecarboxylate obtained in Reference Example 80 and 4'-chloro[1,1'-biphenyl]-4-carboxylic acid.

Elemental analysis for  $C_{30}H_{33}ClN_2O_3 \cdot 0.5H_2O$ 

Calcd. : C, 70.09; H, 6.67; N, 5.45.

Found : C, 70.29; H, 6.50; N, 5.38.

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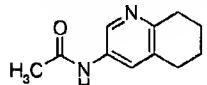
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Melting point: 173 - 176°C

## Reference Example 83

## N-(5,6,7,8-Tetrahydro-3-quinolinyl)acetamide



5

1) Fuming nitric acid (100 ml) was added dropwise to concentrated sulfuric acid solution (200 ml) of 1-methyl-2-pyridone (20.7 g, 190 mmol) at 100°C, which was stirred for 16 hours. The reaction mixture was poured in ice. The resulting precipitate was collected, which was washed with water, to give 1-methyl-3,5-dinitro-2(1H)-pyridinone (3.0 g).

10

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 3.68 (3H, s), 9.01 (1H, d, J=3.0 Hz), 9.61 (1H, d, J=3.0 Hz).

15

2) 1N Methanolic ammonia solution (300 ml) of 1-methyl-3,5-dinitro-2(1H)-pyridinone (3.00g, 15.1mmol) obtained in 1) and 1-morpholino-1-cyclohexene (3.88 ml, 22.6 mmol) was stirred at 70°C for 3 hours. The solvent was distilled out under reduced pressure. The resulting residue was purified by alumina column chromatography (development solvent; ethyl acetate), to give 3-nitro-5,6,7,8-tetrahydroquinoline (2.42 g) as a powder from methanol - water (1:4).

20

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 1.87 (4H, m), 2.90 (4H, m), 8.15 (1H, s), 9.16 (1H, s).

25

3) 10% Palladium-carbon (200 mg) was added to a methanol solution (68 ml) of 3-nitro-5,6,7,8-tetrahydroquinoline (2.41 g, 13.5 mmol) obtained in 2), which was stirred under hydrogen atmosphere for 16 hours.

30

After a catalyst was filtered off, the solvent was distilled out under reduced pressure. The resulting residue was dissolved in pyridine (35 ml). Anhydrous ethyl acetate (1.91 ml, 20.3 mmol) was added to the solution, which was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled out

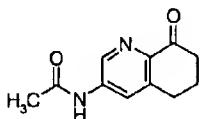
35

under reduced pressure. Diisopropyl ether - n-hexane (1:8) was added to the resulting residue, to give the titled compound (2.48 g) as a colorless powder.

5       <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 1.80-1.87 (4H, m), 2.18 (3H, s), 2.77 (2H, m), 2.87 (2H, m), 7.72 (1H, br), 7.94 (1H, s), 8.24 (1H, s):

Reference Example 84

N-(8-Oxo-5,6,7,8-tetrahydro-3-quinolinyl)acetamide



10       1) m-Chloroperbenzoic acid (3.83 g, 15.5 mmol) was added to a chloroform solution (65 ml) of N-(5,6,7,8-tetrahydro-3-quinolinyl)acetamide (2.46 g, 12.9 mmol) obtained in Reference Example 83 under ice-cooling, which 15 was stirred at room temperature for 16 hours. After the solvent was distilled out under reduced pressure, the residue was powdered with ethyl acetate, to give N-(1-oxide-5,6,7,8-tetrahydro-3-quinolinyl)acetamide (2.00 g).

20       <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ : 1.64 (2H, m), 1.75 (2H, m), 2.04 (3H, s), 2.66 (4H, m), 7.13 (1H, s), 8.56 (1H, s), 10.12 (1H, s).

25       2) Anhydrous ethyl acetate (30 ml) was added to N-(1-oxide-5,6,7,8-tetrahydro-3-quinolinyl)acetamide (1.99 g, 9.65 mmol) obtained in 1), which was stirred at 80°C for 3 hours. The reaction mixture was cooled to room temperature. The solvent was distilled out under reduced pressure, and the resulting residue was purified by alumina column chromatography (development solvent; ethyl acetate). The resulting oily substance was dissolved in methanol (110 ml). 1N Sodium hydroxide (21.5 ml) was added to the solution under ice-cooling, which was stirred at room temperature for 1 hour. The solvent was distilled out under reduced pressure. Chloroform was added to the residue,

which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified by alumina column chromatography (development solvent; ethyl acetate:methanol = 5:1), to give N-(8-hydroxy-5,6,7,8-tetrahydro-3-quinolinyl)acetamide (1.08 g) as a powder from ethyl acetate and diisopropyl ether.

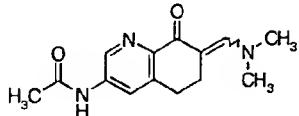
10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.79 (2H, m), 1.96 (1H, m), 2.22 (3H, s), 2.24 (1H, m), 2.82 (2H, m), 4.69 (1H, m), 7.49 (1H, br), 7.92 (1H, s), 8.30 (1H, s).

15 3) Manganese dioxide (4.47 g, 51.4 mmol) was added to chloroform (26 ml) solution of N-(8-hydroxy-5,6,7,8-tetrahydro-3-quinolinyl)acetamide (1.06 g, 5.14 mmol) obtained in 2), which was stirred at room temperature for 1 day. After completion of the reaction, the insoluble matters were filtered off, and the filtrate was concentrated under reduced pressure. Diisopropyl ether and hexane were added to the resulting residue, to give the titled compound (858 mg) as a colorless powder.

20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.20 (2H, m), 2.26 (3H, s), 2.77 (2H, m), 3.03 (2H, m), 8.10 (1H, br), 8.39 (1H, s), 8.42 (1H, s).

25 Reference Example 85

N-[7-[(Dimethylamino)methylidene]-8-oxo-5,6,7,8-tetrahydro-3-quinolinyl]acetamide



30 The titled compound was obtained by carrying out the same operation as in Reference Example 47, using N-(8-oxo-5,6,7,8-tetrahydro-3-quinolinyl)acetamide obtained in Reference Example 84.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.09 (3H, s), 2.78 (2H, m), 2.85 (2H, m), 3.10 (6H, s), 7.55 (1H, s), 8.01 (1H, s), 8.56 (1H, s).

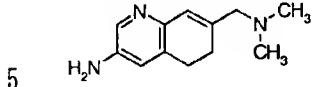
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## Reference Example 86

N-[(3-Amino-5,6-dihydro-7-quinolinyl)methyl]-N,N-dimethylamine

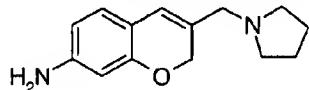


The titled compound was obtained by carrying out the same operation as in Reference Example 41-2), using N-[7-[(dimethylamino)methylidene]-8-oxo-5,6,7,8-tetrahydro-3-quinolinyl]acetamide obtained in Reference Example 85.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 2.23 (6H, s), 2.33 (2H, t, J=8.1 Hz), 2.78 (2H, t, J=8.1 Hz), 2.99 (2H, s), 3.59 (2H, br), 6.43 (1H, s), 6.74 (1H, d, J=2.5 Hz), 7.84 (1H, d, J=2.5 Hz).

## 15 Reference Example 87

3-(1-Pyrrolidinylmethyl)-2H-chromen-7-amine



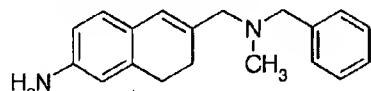
The titled compound was obtained as an oily substance by carrying out the same operations as in Example 41-1), Reference Example 52 and Example 41-2) in this order, using 7-acetylamino-3,4-dihydrochromen-4-one.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.77-179 (4H, m), 2.45-2.47 (4H, m), 3.11 (2H, s), 3.66 (2H, s), 4.74 (2H, s), 6.14-6.21 (3H, m), 6.75 (1H, d, J = 7.8 Hz).

25

## Reference Example 88

6-[(N-Benzyl-N-methylamino)methyl]-7,8-dihydro-2-naphthalenamine



The titled compound was obtained as an oily substance by carrying out the same operation as in Reference Example 52, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-

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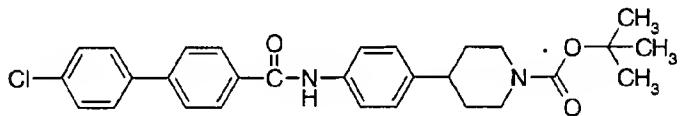
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1-tetralone obtained in Example 41-1).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.17 (3H, s), 2.35 (2H, t, J = 8.1 Hz),  
2.73 (2H, t, J = 8.1 Hz), 3.04 (2H, s), 3.48 (2H, s), 3.58  
(2H, s), 6.29 (1H, s), 6.44 -6.46 (2H, m), 6.82 (1H, d, J  
5 = 8.1 Hz), 7.03-7.45 (5H, m).

## Reference Example 89

4'-Chloro-N-[4-(4-piperidinyl)phenyl][1,1'-biphenyl]-  
4-carboxamide



10

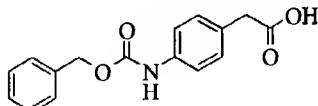
An ethanol solution (30 ml) of tert-butyl 4-(4-nitrophenyl)-1-piperidinecarboxylate (1.7 g) was subjected to catalytic hydrogenation using 10% palladium carbon (0.2 g) as a catalyst under normal temperature and normal pressure. After the catalyst was filtered off, the filtrate was concentrated to give tert-butyl 4-(4-aminophenyl)-1-piperidinecarboxylate as a viscous oily substance. The titled compound (2.2 g) was obtained as colorless crystals, by carrying out the same operation as in Example 1, using the resulting oily substance and 4'-chloro[1,1'-biphenyl]-4-carboxylic acid (1.43 g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>+ DMSO-d<sub>6</sub>) δ : 1.05-1.32 (11H, m), 1.38-1.50 (2H, m), 2.20-2.50 (3H, m), 3.75-3.90 (2H, m), 6.81 (2H, d, J=8.4 Hz), 7.07 (2H, d, J=8.4 Hz), 7.20-7.36 (6H, m), 7.69 (2H, d, J=8.1Hz), 9.44 (1H, s).

Melting point: 232 - 233°C (crystallization solvent : ethyl acetate)

## Reference Example 90

30 2-[4-[(Benzyl)oxycarbonyl]amino]phenylethyl acetate



To an ethyl acetate (100 ml) suspension of 4-

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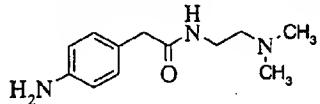
aminophenylethyl acetate (10 g), saturated aqueous sodium bicarbonate solution (100 ml) was added, and further, benzyloxycarbonyl chloride (12.3 ml) was added dropwise under ice-cooling. After stirring for 1 hour,

5 hydrochloric acid was added to the reaction mixture to make it acidic, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized from ethyl acetate - hexane, to give the titled compound (17.3 g).  
10 Melting point: 148 - 149°C

Reference Example 91

2-(4-Aminophenyl)-N-[2-

15 (dimethylamino)ethyl]acetamide



Pd-C (1 g) was added to a methanol (140 ml) solution of benzyl 4-[2-[2-(dimethylamino)ethyl]amino]-2-oxoethyl phenylcarbamate (10 g), which was stirred under 20 hydrogen atmosphere for 1 hour. Pd-C was removed, and the filtrate was concentrated. The residue was purified by alumina column chromatography (development solvent; ethyl acetate:hexane = 1:1), to give the titled compound (6.63 g) as an oily substance.

25 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 2.16 (6H, s), 2.05 (3H, s), 2.30-2.36 (2H, t, J=6.2 Hz), 3.23-3.32 (2H, dd, J=11.4, 6.2 Hz), 3.44 (2H, s), 6.00 (1H, s), 6.63-6.67 (2H, m), 7.00-7.07 (2H, m).

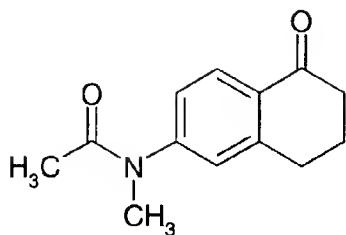
30 Reference Example 92

N-Methyl-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)acetamide

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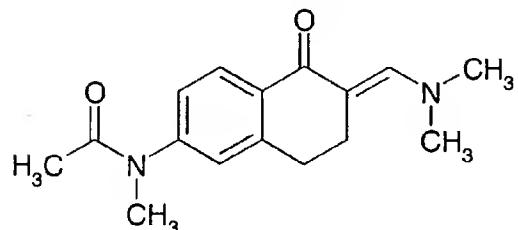
6-Acetamido-1-tetralone (10.0 g, 49.2 mmol) was dissolved in tetrahydrofuran (100 ml). Sodium hydride (oil, 3.0 g) was added to the solution, which was refluxed with heating under nitrogen atmosphere for 2 hours. After cooling, methyl iodide (30 ml) was added to the reaction mixture, which was refluxed with heating under nitrogen atmosphere for 2 hours. The reaction mixture was concentrated. Ethyl acetate and water were added to the residue, and extraction was conducted. The ethyl acetate layer was concentrated, and the residue was purified by alumina column chromatography (development solvent; ethyl acetate:n-hexane = 33:67 ~ 50:50). The product was concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate - diisopropyl ether, to give the titled compound (4.3 g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.96 (3H, brs), 2.18 (2H, m), 2.69 (2H, t, J=6.1 Hz), 2.99 (2H, t, J=5.9 Hz), 3.29 (3H, s), 7.01-7.15 (2H, m), 8.08 (1H, d, J=8.1 Hz).

20

Reference Example 93

N-[6-[(Dimethylamino)methylidene]-5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl]-N-methylacetamide



25

N-Methyl-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)acetamide (4.3 g, 19.8 mmol) obtained in Reference Example 92 was dissolved in N,N-

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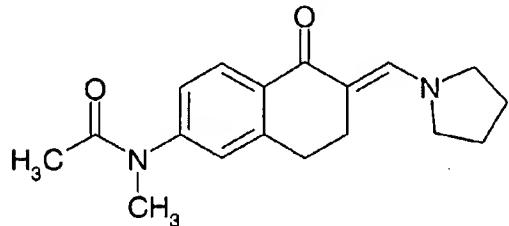
dimethylformamide dimethylacetal (50 ml), which was refluxed with heating under nitrogen atmosphere for 15 hours. The reaction mixture was concentrated, and the residue was washed with ethyl acetate and diisopropyl ether, to give the titled compound (3.9 g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.93 (3H, brs), 2.84 (2H, dd, J=7.5, 5.6 Hz), 2.95 (2H, dd, J=7.5, 5.6 Hz), 3.16 (6H, s), 3.28 (3H, s), 6.99 (1H, s), 7.10 (1H, dd, J=8.1, 2.0 Hz), 7.75 (1H, s), 8.07 (1H, d, J=8.1 Hz).

10

**Reference Example 94**

N-Methyl-N-[5-oxo-6-[1-pyrrolidinylmethylidene]-5,6,7,8-tetrahydro-2-naphthalenyl]acetamide



15 N-[6-[(Dimethylamino)methylidene]-5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl]-N-methylacetamide (5.7 g, 20.9 mmol) obtained in Reference Example 93 was dissolved in pyrrolidine (50 ml), which was refluxed with heating under nitrogen atmosphere for 3.5 hours. Then, ethyl acetate and water were added to the reaction mixture, and extraction was conducted. The ethyl acetate layer was concentrated, and the residue was recrystallized from ethyl acetate - diisopropyl ether, to give the titled compound (4.0 g, yield : 64%).

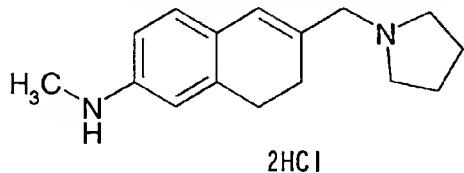
20

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.94 (7H, m), 2.84 (2H, dd, J=7.0, 5.6 Hz), 2.97 (2H, dd, J=7.0, 5.6 Hz), 3.28 (3H, s), 3.63 (4H, m), 6.98 (1H, s), 7.10 (1H, dd, J=8.1, 2.0 Hz), 7.95 (1H, s), 8.08 (1H, d, J=8.1 Hz).

30 Reference Example 95

N-Methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-

## nephthalenamine dihydrochloride



N-Methyl-N-[5-oxo-6-[1-pyrrolidinylmethylidene]-5,6,7,8-tetrahydro-2-naphthalenyl]acetamide (4.0 g, 13.4 mmol) obtained in Reference Example 94 was dissolved in methanol - ethyl acetate (10:1, 220 ml). 10% Palladium on carbon (50% wet, 0.4 g) was added to the solution, which was ice cooled. Stirring was begun under hydrogen atmosphere, and stirring was conducted for 2 days while returning the temperature of the reaction mixture to room temperature. A catalyst was filtered off, the reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. Extraction was conducted using 1N hydrochloric acid. The extract was made alkaline with 4N sodium hydroxide solution, and extraction was conducted using ethyl acetate. The extract was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (100 ml) and 5N hydrochloric acid (100 ml), which was refluxed with heating for 13 hours. The reaction mixture was concentrated. Ethyl acetate and saturated aqueous sodium carbonate solution were added to the residue, and extraction was conducted. The ethyl acetate layer was concentrated. 4N Hydrogen chloride - ethyl acetate solution was added to the resulting oily substance, which was concentrated. The residue was recrystallized from methanol - ethyl acetate, to give the titled compound (2.8 g, yield : 66%).  
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 1.98 (4H, m), 2.45 (4H, m), 2.81 (5H, m), 3.01 (2H, brd), 3.44 (2H, brd), 3.86 (2H, d, J=5.0 Hz), 7.02-7.10 (3H, m), 10.89 (1H, brs).

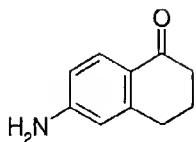
## Reference Example 96

6-Amino-3,4-dihydro-1-(2H)-naphthalenone

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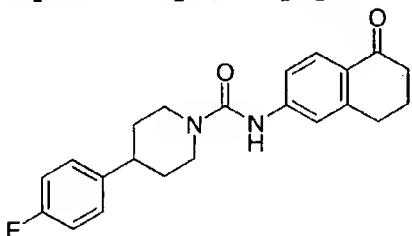


Concentrated hydrochloric acid (250 ml) was added to 6-acetamido-1-tetralone (20.0 g, 98.4 mmol), which was stirred at 100°C for 1 hour. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The residue was powdered with ethyl acetate and isopropyl ether, to give the titled compound (14.5 g).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 2.07 (2H, m), 2.57 (2H, m), 2.83 (2H, m), 4.10 (2H, br), 6.42 (1H, d, J=2.2 Hz), 6.53 (1H, dd, J=2.2, 8.4 Hz), 7.89 (1H, d, J=8.4 Hz).

15

Reference Example 97  
4-(4-Fluorophenyl)-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)-1-piperidinecarboxamide



Pyridine (9.95 ml, 123 mmol) and 4-nitrophenyl chloroformate (12.4 g, 61.5 mmol) was added to a tetrahydrofuran (300 ml) solution of 6-amino-3,4-dihydro-1(2H)-naphthalenone (9.92 g, 61.5 mmol) obtained in Reference Example 96, which was stirred at room temperature for 3 hours. The solvent was distilled out under reduced pressure. 1N Hydrochloric acid was added to the residue to powder, which was washed with ethanol. 4N Aqueous sodium hydroxide solution was added to a dimethylsulfoxide (33 ml) solution of the resulting 4-nitrophenyl-5-oxo-

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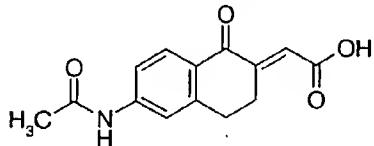
154

5,6,7,8-tetrahydro-2-naphthalenylcarbamate (2.20 g, 6.74 mmol) and 4-(4-fluorophenyl)piperidine hydrochloride (1.60 g, 7.42 mmol), which was stirred at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, which was washed with 1N hydrochloric acid, aqueous potassium hydrogencarbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was distilled out under reduced pressure. The resulting residue was purified by alumina B column chromatography (development solvent; ethyl acetate), and powdered with isopropyl ether and hexane, to give the titled compound (1.89 g).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 1.72 (2H, m), 1.92 (2H, m), 2.11 (2H, m), 2.61 (2H, m), 2.72 (1H, m), 2.93 (2H, m), 3.01 (2H, m), 4.23 (2H, m), 6.67 (1H, s), 7.00 (2H, m), 7.12 (3H, m), 7.61 (1H, s), 7.97 (1H, d, J=8.4 Hz).

## Reference Example 98

[6-(Acetylamino)-1-oxo-3,4-dihydro-2(1H)-naphthalenylidene]acetic acid

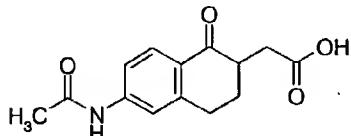


0.5N Aqueous sodium hydroxide solution (190 ml) was added to an aqueous solution (60 ml) of 6-acetamido-1-tetralone (5.00 g, 24.6 mmol) and glyoxylic acid (9.05 g, 98.5 mmol) under ice-cooling, which was stirred at 60°C for 16 hours. After cooling, concentrated hydrochloric acid was added to the reaction mixture. The precipitated crystals were collected, which was washed with water, to give the titled compound (3.73 g).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ : 2.10 (3H, s), 2.95 (2H, m), 3.28 (2H, m), 6.63 (1H, s), 7.53 (1H, d, J=8.7Hz), 7.67 (1H, s), 7.91 (1H, d, J=8.7Hz), 10.32 (1H, s), 12.89 (1H, br).

## Reference Example 99

[6-(Acetylamino)-1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl]acetic acid

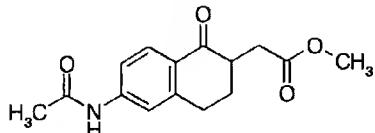


5        70% Acetic acid - water solution (35 ml) of [6-(acetylamino)-1-oxo-3,4-dihydro-2(1H)-naphthalenyliden]acetic acid (3.50 g, 13.5 mmol) obtained in Reference Example 98 and zinc powder (2.1 g) was stirred at 100°C for 30 minutes. After cooling, zinc powder was  
10      filtered. Ethyl acetate was added to the filtrate, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column  
15      chromatography (development solvent; ethyl acetate : methanol = 10:1), and powdered with ethyl acetate and isopropyl ether, to give the titled compound (2.51 g).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.85-2.15 (2H, m), 2.08 (3H, s), 2.38 (1H, m), 2.71 (1H, m), 2.88 (2H, m), 3.05 (1H, m), 7.46 (1H, d, J=8.7Hz), 7.60 (1H, s), 7.80 (1H, d, J=8.7Hz), 10.21 (1H, s), 12.09 (1H, br).

20

## Reference Example 100

Methyl [6-(acetylamino)-1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl]acetate



25        Methyl iodide (0.18 ml, 2.87 mmol) was added to a dimethylformamide solution (10 ml) of [6-(acetylamino)-1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl]acetic acid (500 mg, 1.91 mmol) obtained in Reference Example 99 and potassium carbonate (529 mg, 3.82 mmol), which was stirred  
30

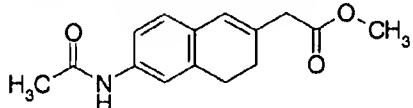
at room temperature for 16 hours. Ethyl acetate was added to the reaction mixture, which was washed with aqueous sodium thiosulfate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and 5 then the solvent was distilled out under reduced pressure.

The resulting oily substance was purified by alumina B column chromatography (development solvent; ethyl acetate), to give the titled compound (527 mg).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.98 (1H, m), 2.20 (3H, s), 2.23 (1H, m), 10 2.47 (1H, m), 3.30 (4H, m), 3.73 (3H, s), 7.21 (1H, d, J=8.7Hz), 7.50-7.80 (2H, m), 7.97 (1H, d, J=8.7Hz).

Reference Example 101

Methyl [6-(acetylamino)-3,4-dihydro-2-15 naphthalenyl]acetate



Sodium borohydride (72.4 mg, 1.91 mmol) was added to a methanol solution (10ml) of methyl [6-(acetylamino)-1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl]acetate (527 mg, 1.91 mmol) obtained in Reference Example 100 under ice-cooling, which was stirred for 1 hour. Ethyl acetate was 20 added to the reaction mixture, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was 25 distilled out under reduced pressure. The resulting oily substance was purified by alumina B column chromatography (development solvent; ethyl acetate). Concentrated sulfuric acid (0.14 ml) was added to an acetic acid solution (7 ml) of the oil (404 mg, 1.46 mmol), which was stirred 30 at 40°C for 5 hours. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was

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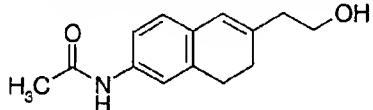
157

distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent;hexane:ethyl acetate = 1:1), to give the titled compound (251 mg).

5     <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 2.16 (3H, s), 2.32 (2H, t, J=8.1Hz) , 2.82 (2H, t, J=8.1Hz), 3.21 (2H, s), 3.71 (3H, s), 6.30 (1H, s), 6.93 (1H, d, J=8.1Hz), 7.19 (2H, m) , 7.33 (1H, s).

Reference Example 102

10    N-[6-(2-Hydroxyethyl)-7,8-dihydro-2-naphthalenyl]acetamide

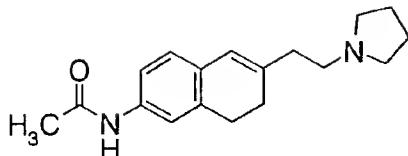


Lithium aluminum hydride (242 mg, 6.38 mmol) was added to a tetrahydrofuran solution (16 ml) of methyl [6-(acetylamino)-3,4-dihydro-2-naphthalenyl]acetate (827 mg, 3.19 mmol) obtained in Reference Example 101 under ice-cooling, which was stirred at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, which was washed with 1N hydrochloric acid and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The residue was powdered with isopropyl ether, to give the titled compound (364 mg).

15    <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 1.43 (1H, m), 2.16 (3H, s), 2.26 (2H, t, J=8.1Hz) , 2.46 (2H, t, J=6.3Hz) , 2.81 (2H, t, J=8.1Hz), 3.78 (2H, m), 6.28 (1H, s), 6.94 (1H, d, J=8.1Hz), 7.08 (1H, br), 7.17 (1H, d, J=8.1Hz), 7.35 (1H, s).

Reference Example 103

20    N-[6-[2-(1-Pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl]acetamide



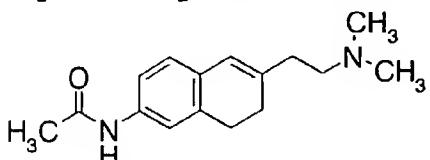
Methanesulfonyl chloride (0.131 ml, 1.69 mmol) was added to a dimethylformamide solution (7 ml) of N-[6-(2-hydroxyethyl)-7,8-dihydro-2-naphthalenyl]acetamide (355 mg, 1.53 mmol) obtained in Reference Example 102 and triethylamine (0.235 ml, 1.69 mmol) under ice-cooling, which was stirred for 30 minutes. Pyrrolidine (0.384 ml, 4.60 mmol) was added to the reaction mixture, which was stirred at 60 °C for 4 hours. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, and extraction was conducted using 1N hydrochloric acid. Potassium carbonate was added to the extract to make it alkaline, and extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was distilled out under reduced pressure. The resulting residue was purified by alumina column chromatography (development solvent; ethyl acetate), to give the titled compound (294 mg).

10      20      15      25      20      25

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 1.79 (4H, m), 2.16 (3H, s), 2.25 (2H, m), 2.41 (2H, m), 2.55 (4H, m), 2.62 (2H, m), 2.78 (2H, m), 6.20 (1H, s), 6.91 (1H, d, J=8.1Hz), 7.18 (1H, d, J=7.8Hz), 7.32 (2H, m).

Reference Example 104

N-[6-[2-(Dimethylamino)ethyl]-7,8-dihydro-2-naphthalenyl]acetamide



Methanesulfonyl chloride (0.0393 ml, 0.469 mmol) was added to a dimethylformamide solution (2 ml) of N-[6-

30

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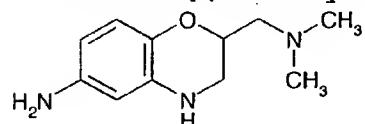
159

(2-hydroxyethyl)-7,8-dihydro-2-naphthalenyl]acetamide (102 mg, 0.426 mmol) obtained in Reference Example 102 and triethylamine (0.0652 ml, 0.469 mmol) under ice-cooling, which was stirred for 30 minutes. A tetrahydrofuran 5 solution (0.64 ml) of 2N dimethylamine was added to the reaction mixture, which was stirred at 60°C for 5 hours. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, and extraction was conducted using 1N hydrochloric acid. Potassium carbonate 10 was added to the extract to make it alkaline, and extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was distilled out under reduced pressure. The resulting residue was 15 purified by alumina column chromatography (development solvent; ethyl acetate), to give the titled compound (57.5 mg).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 2.15 (3H, s), 2.24 (2H, m), 2.29 (6H, s), 2.36 (2H, m), 2.48 (2H, m), 2.78 (2H, m), 6.20 (1H, s), 6.90 (1H, d, J=8.1Hz), 7.20 (1H, d, J=8.1Hz), 7.35 (1H, s), 7.76 (1H, br).

## Reference Example 105

## 6-Amino-2-[(dimethylamino)methyl]-1,4-benzoxazine



25 1) 2-Ethoxycarbonyl-6-nitro-1,4-benzoxazine (7.20 g, 0.029 mol) obtained by a known method by documents (Journal of heterocyclic chemistry, 19(5), p.1189 (1982)) was dissolved in methanol (50 ml). Sodium borohydride 30 (1.08 g, 0.029 mol) was added to the solution, which was stirred for 2 hours. The reaction mixture was concentrated. Ethyl acetate and aqueous potassium hydrogencarbonate solution were added to the residue, and extraction was conducted. The organic layer was washed

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with water, and concentrated. A mixed solution of ethyl acetate and n-hexane (1:5) was added to the residue for crystallization. The crystallized product was collected by filtration, to give 2-hydroxymethyl-6-nitro-1,4-  
5 benzoxazine (3.10 g) as a red powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.96 (1H, m), 3.34-3.49 (2H, m), 3.80-3.90 (2H, m), 4.09 (1H, brs), 4.30-4.40 (1H, m), 6.86 (1H, d, J=8.6 Hz), 7.50 (1H, d, J=2.8 Hz), 7.59 (1H, dd, J=2.8, 8.6 Hz).

10 2) 2-Hydroxymethyl-6-nitro-1,4-benzoxazine (1.00 g, 4.76 mmol) obtained in 1) and triethylamine (708 mg, 7.00 mmol) was dissolved in DMF (30 ml). Methanesulfonyl chloride (545 mg, 4.76 mmol) was added to the solution, which was stirred for 30 minutes. 50% Aqueous

15 dimethylamine solution (3 ml) was added to the reaction mixture, which was stirred at 70°C for 4 hours. Ethyl acetate and water were added to the mixture, and extraction was conducted. The organic layer was washed, and concentrated. The residue was subjected to alumina column chromatography, and eluted with ethyl acetate : n-hexane (40:60), to give 2-[(dimethylamino)methyl]-6-nitro-1,4-  
20 benzoxazine (790 mg) as a colorless oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.33 (6H, s), 2.47-2.67 (2H, m), 3.19-3.25 (1H, m), 3.46-3.52 (1H, m), 4.09 (1H, brs), 4.30-4.35 (1H, m), 6.86 (1H, d, J=8.9 Hz), 7.48 (1H, d, J=2.8 Hz), 7.57 (1H, dd, J=2.8, 8.9 Hz).

30 3) 2-[(Dimethylamino)methyl]-6-nitro-1,4-benzoxazine (760 mg, 3.2 mmol) obtained in 2) was dissolved in methanol (10 ml). Concentrated hydrochloric acid (3 ml) and iron powder (0.80 g) were added to the solution, which was stirred for 2 hours. The reaction mixture was concentrated. 1N Aqueous sodium hydroxide solution and ethyl acetate was added to the residue, and extraction was conducted. The organic layer was concentrated. The residue was subjected to alumina column chromatography, and eluted with ethyl acetate : n-hexane (20:80), to give the

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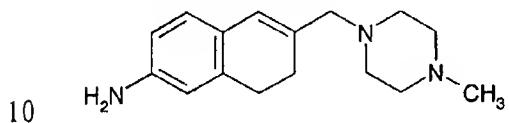
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titled compound (430 mg) as a colorless oily substance.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.31 (6H, s), 2.41-2.62 (2H, m), 3.12-3.17 (1H, m), 3.36-3.41 (1H, m), 3.30-3.50 (2H, brs), 3.67 (1H, brs), 4.12-4.21 (1H, m), 5.99 (1H, d, J=2.5 Hz), 6.03 (1H, dd, J=2.5, 8.4 Hz), 6.65 (1H, d, J=8.4 Hz).

## Reference Example 106

6-[(4-Methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine



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The titled compound was obtained by carrying out the same operation as in Reference Example 52, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone obtained in Example 41-1).

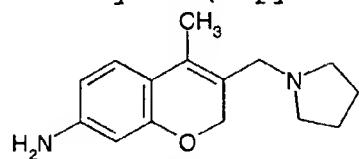
15

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 2.27 (2H, t, J=8.1 Hz), 2.29 (3H, s), 2.45 (8H, bs), 2.72 (2H, t, J=8.1 Hz), 3.03 (2H, s), 3.60 (2H, s), 6.26 (1H, s), 6.45-6.47 (2H, m), 6.80-6.83 (1H, m).

## Reference Example 107

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4-Methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine



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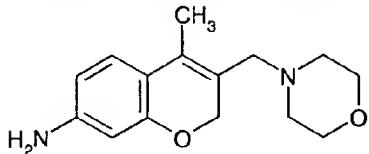
The titled compound was obtained by carrying out the same operations as in Example 41-1) and Reference Example 69 in this order, using 1-acetylamo-3,4-dihydrochromen-1-one.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 1.73-1.83 (4H, m), 1.99 (3H, s), 2.46-2.51 (4H, m), 3.22 (2H, s), 3.70 (2H, bs), 4.66 (2H, s), 6.18 (1H, d, J=2.2 Hz), 6.26 (1H, dd, J=2.2 Hz, 8.1 Hz), 7.00 (1H, d, J=8.1 Hz).

30

## Reference Example 108

## 4-Methyl-3-(4-morpholinylmethyl)-2H-chromen-7-amine



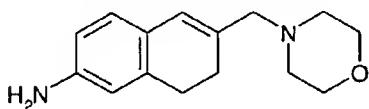
The titled compound was obtained by carrying out the same operations as in Example 41-1) and Reference Example 5 69 in this order, using 1-acetylamo-3,4-dihydrochromen-1-one.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 1.98 (3H, s), 2.41-2.44 (4H, m), 3.08 (2H, s), 3.66-3.69 (6H, m), 4.62 (2H, s), 6.18 (1H, d, J=2.2 Hz), 6.26 (1H, dd, J=2.2 Hz, 8.1 Hz), 7.00 (1H, d, J=8.1 Hz).

10

## Reference Example 109

## 6-(4-Morpholinylmethyl)-7,8-dihydro-2-naphthalenamine

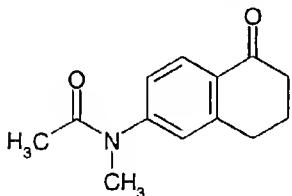


The titled compound was obtained by carrying out the 15 same operations as in Reference Example 52, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone obtained in Example 41-1).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.28 (2H, t, J=7.8 Hz), 2.42 (4H, t, J=4.4 Hz), 2.72 (2H, t, J=7.8 Hz), 3.01 (2H, s), 3.60 (2H, brs.), 20 3.70 (4H, t, J=4.4 Hz), 6.26 (1H, s), 6.46 (2H, m), 6.82 (1H, d, J=8.7 Hz).

## Reference Example 110

N-Methyl-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)acetamide



6-Acetamido-1-tetralone (13.7 g, 67.4 mmol) was dissolved in tetrahydrofuran (40 ml). Sodium

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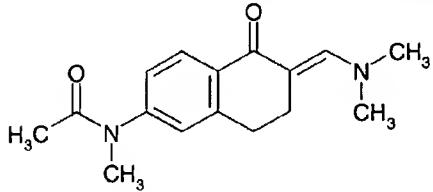
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hydride(oil)(2.40 g, 101 mmol) was added to the solution, which was refluxed with heating for 2.5 hours. After cooling, methyl iodide(20 ml)was added to the reaction mixture, which was stirred at 40°C for 15 hours. The 5 reaction mixture was poured into a cold water, and extraction was conducted using ethyl acetate. The extract was washed with 1N hydrochloric acid and 1 N aqueous sodium hydroxide solution. The ethyl acetate layer was concentrated. The residue was purified by alumina column 10 chromatography (development solvent ; ethyl acetate:n-hexane = 50:50 ~ 100:0) . The eluent was concentrated under reduced pressure. The resulting residue was recrystallized from ethyl acetate - diisopropyl ether, to give the titled compound(8.3 g).

15  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.96 (3H, s), 2.19(2H, m), 2.69 (2H, t,  $J=6.2$  Hz), 2.99 (2H, t,  $J=5.9$  Hz), 3.29 (3H, s), 7.10-7.15 (2H, m), 8.09 (1H, d,  $J=8.4$  Hz).

## Reference Example 111

20 N-[6-[(E)-(Dimethylamino)methylidene]-5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl]-N-methylacetamide



25 N-Methyl-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)acetamide (4.3 g, 19.8 mmol) obtained in Reference Example 110 was dissolved in N,N-dimethylformamide-dimethylacetal(50 ml), which was refluxed with heating under nitrogen atmosphere for 15 hours. The reaction mixture was concentrated under reduced pressure. The resulting residue was washed with 30 ethyl acetate - diisopropyl ether, to give the titled compound(3.9 g).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.93 (3H, s), 2.86 (2H, t,  $J=7.3$  Hz), 2.95

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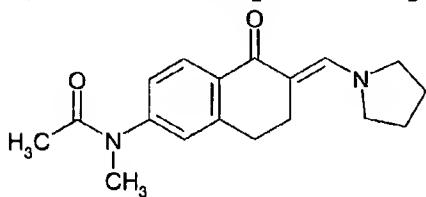
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(2H, t, J=7.3 Hz), 3.16 (6H, s), 3.28 (3H, s), 6.99 (1H, s), 7.09 (1H, d, J=8.1 Hz), 7.75 (1H, s), 8.07 (1H, d, J=8.1 Hz).

## 5 Reference Example 112

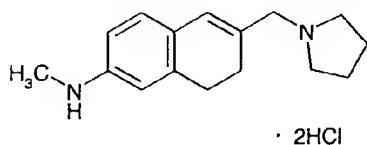
N-Methyl-N-[5-oxo-6-((E)-1-pyrrolidinylmethylidene)-5,6,7,8-tetrahydro-2-naphthalenyl]acetamide



- 10 N-[6-[(E)-(dimethylamino)methylidene]-5-oxo-  
5,6,7,8-tetrahydro-2-naphthalenyl]-N-methylacetamide  
(5.7 g, 20.9 mmol) obtained in Reference Example 111 was dissolved in pyrrolidine (50 ml), which was refluxed with heating under nitrogen atmosphere for 3.5 hours. The reaction mixture was poured into cold water, and extraction  
15 was conducted using ethyl acetate. The ethyl acetate layer was concentrated. The resulting residue was recrystallized from ethyl acetate - diisopropyl ether, to give the titled compound (4.0 g).  
1H-NMR (CDCl<sub>3</sub>) δ : 1.93-1.96 (7H, m), 2.85 (2H, t, J=6.7 Hz),  
20 2.96 (2H, t, J=6.7 Hz), 3.28 (3H, s), 3.63 (4H, m), 6.99 (1H, s), 7.10 (1H, dd, J=8.4, 2.0 Hz), 7.95 (1H, s), 8.08 (1H, d, J=8.4 Hz).

## Reference Example 113

- 25 N-Methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine dihydrochloride



- 30 N-Methyl-N-[5-oxo-6-((E)-1-pyrrolidinylmethylidene)-5,6,7,8-tetrahydro-2-naphthalenyl]acetamide (4.0 g, 13.4 mmol) obtained in

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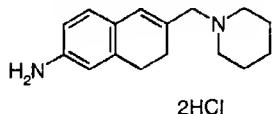
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Reference Example 112 was dissolved in methanol - acetic acid(10:1, 220 ml). 10% Palladium on carbon (0.4 g) was added to the solution, which was stirred under hydrogen atmosphere for 48 hours. The catalyst was filtered off, and 5 the reaction mixture was concentrated under reduced pressure. Ethyl acetate and 1N hydrochloric acid were added to the residue, and extraction was conducted. After the water layer was made alkaline with 4N aqueous sodium hydroxide solution, extraction was conducted using ethyl 10 acetate. The ethyl acetate layer was concentrated. Tetrahydrofuran - 5N hydrochloric acid (50:50, 200 ml) was added to the resulting residue, which was refluxed with heating for 13 hours. The reaction mixture was concentrated. Ethyl acetate and saturated aqueous sodium 15 carbonate solution was added to the residue, and extraction was conducted. 4N Hydrogen chloride - ethyl acetate solution was added to the ethyl acetate layer, which was concentrated under reduced pressure. The resulting residue was recrystallized from methanol - ethyl acetate, 20 to give the titled compound(2.8 g).

$^1\text{H-NMR}$  (DMSO-d<sub>6</sub>)  $\delta$  : 1.98 (4H, m), 2.45 (4H, m), 2.81 (5H, m), 3.01 (2H, m), 3.44 (2H, m), 3.85 (1H, s), 3.86 (1H, s), 6.67 (1H, s), 7.02-7.10 (3H, m), 10.90 (1H, brs.).

25 Reference Example 114

6-(1-Piperidinylmethyl)-7,8-dihydro-2-naphthalenamine dihydrochloride



The titled compound was obtained by carrying out the 30 same operation as in Reference Example 52, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone obtained in Example 41-1).

$^1\text{H-NMR}$  (DMSO-d<sub>6</sub>)  $\delta$  : 1.39 (1H, m), 1.80 (5H, m), 2.50 (5H, m), 2.83 (4H, m), 3.35-3.38 (2H, m), 3.79 (2H, s), 6.70 (1H,

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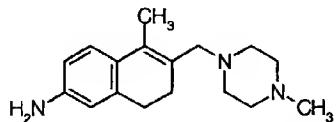
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s), 7.05-7.13 (3H, m), 10.40 (1H, brs).

Reference Example 115

5-Methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-

dihydro-2-naphthalenamine

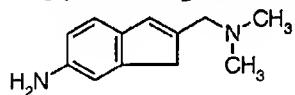


The titled compound was obtained by carrying out the same operation as in Reference Example 69, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone obtained in Example 41-1).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 2.02 (3H, s), 2.27 (2H, t, J=8.1 Hz), 2.27 (3H, s), 2.44 (8H, bs), 2.63 (2H, t, J=8.1 Hz), 3.12 (2H, s), 3.61 (2H, s), 6.48-6.54 (2H, m), 7.08 (1H, d, J=7.8 Hz).

15 Reference Example 116

2-[(Dimethylamino)methyl]-1H-inden-6-amine



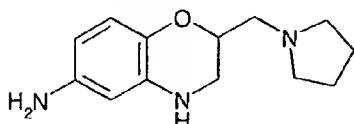
The titled compound was obtained by carrying out the same operation as in Example 41-2), using N-[2-[(E)-(dimethylamino)methylidene]-1-oxo-2,3-dihydro-1H-inden-5-yl]acetamide obtained in Reference Example 47.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 2.24 (6H, s), 3.26 (2H, s), 3.33 (2H, s), ca.3.5 (2H, br), 6.58 (2H, m), 6.81 (1H, s), 7.08 (1H, d, J=8.1 Hz).

25

Reference Example 117

6-Amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine



30 A mixture of 6-nitro-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine and 4-(methylsulfonyl)-

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6-nitro-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine was obtained by carrying out the same operation as in Reference Example 105-2), using 2-hydroxymethyl-6-nitro-3,4-dihydro-2H-1,4-benzoxazine obtained in 5 Reference Example 105-1).

The titled compound was obtained by carrying out the same operation as in Reference Example 105-3), using the mixture obtained above.

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.76-1.81 (4H, m), 2.50-2.70 (4H, m), 2.70 (2H, d,  $J=6.3\text{Hz}$ ), 3.13-3.20 (1H, m), 3.20-3.40 (2H, brs), 3.39-3.43 (1H, m), 3.66 (1H, brs), 4.11-4.21 (1H, m), 5.99 (1H, d,  $J=2.7\text{Hz}$ ), 6.03 (1H, dd,  $J=2.7, 8.4\text{ Hz}$ ), 6.64 (1H, d,  $J=8.4\text{ Hz}$ ).

15 Reference Example 118

6-Amino-4-(methylsulfonyl)-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine



20 The titled compound was obtained by carrying out the same operation as in Reference Example 105-3), using the mixture of 6-nitro-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine and 4-(methylsulfonyl)-6-nitro-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine obtained in Reference Example 117.

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.70-1.80 (4H, m), 2.50-2.70 (4H, m), 2.73 (2H, d,  $J=6.0\text{Hz}$ ), 2.95 (3H, s), 3.21-3.29 (1H, m), 2.80-3.10 (2H, brs), 4.10-4.21 (1H, m), 4.26-4.32 (1H, m), 6.43 (1H, dd,  $J=2.7, 8.4\text{ Hz}$ ), 6.77 (1H, d,  $J=8.4\text{ Hz}$ ), 7.11 (1H, d,  $J=2.7\text{Hz}$ ).

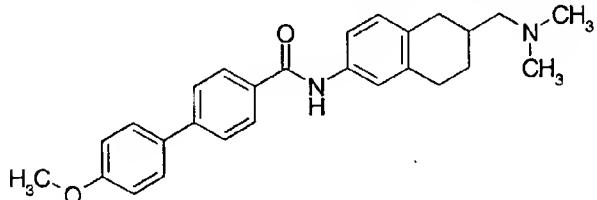
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## Example 1

N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-(4'-methoxybiphenyl-4-yl)carboxamide



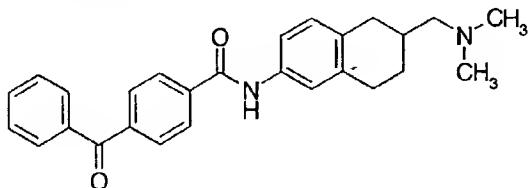
5 DMF solution (0.25 ml) of 2M HOBT, DMF solution (0.30 ml) of 2M WSCD, triethylamine (0.14 ml) and DMAP (0.132 g) were added to DMF solution (3 ml) of 6-amino-2-(N,N-dimethylamino)methyltetralin (0.139 g) and 4-(4-methoxy phenyl)benzoic acid (0.118 g). After the reaction mixture  
10 was stirred at room temperature for 12 hours, 10% potassium carbonate solution was added, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting crude crystal  
15 was washed with diethyl ether, which was recrystallized using ethyl acetate-hexane, to give the titled compound (0.124 g).

Melting point: 170 - 175°C.

20 Compounds described in the following Examples 2 and 3 were produced in the same manner as in Example 1.

## Example 2

4-Benzoyl-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide



Melting point: 193 - 196°C (recrystallization solvent: ethyl acetate-hexane)

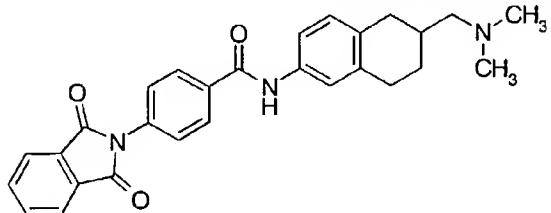
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## Example 3

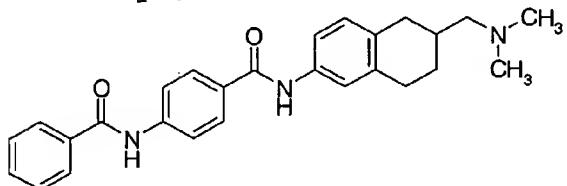
N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl) benzamide



5 Melting point: 235 - 240°C (washed with diethyl ether)

## Example 4

4-(Benzoylamino)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide



10

6-Amino-2-(N,N-dimethylamino)methyltetralin hydrochloride (139 mg), 4-benzoylaminobenzoic acid (121 mg), WSCD (0.13 ml), HOBT (92 mg), triethylamine (0.14 ml) and DMAP (61 mg) were added to DMF (4 ml). After the reaction mixture was shaken at room temperature for 20 hours using a shaker, the reaction mixture was poured into water, and extraction was conducted using ethyl acetate-THF (1:1). The organic layer was washed with water, saturated sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting crude crystal was washed with hexane, to give the titled compound (181 mg).

15

20

25

Melting point : 241 - 242°C

Washing solvent : hexane

25

Compounds described in the following Examples 5 to 14 were produced in the same manner as in Example 4.

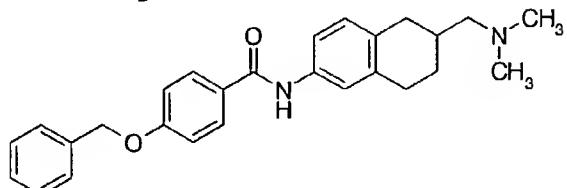
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**Example 5**

4-(BenzylOxy)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide

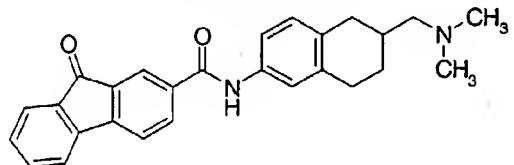


5 Melting point : 135 - 136°C

Washing solvent : hexane

**Example 6**

N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-9-oxo-9H-fluoren-2-carboxamide

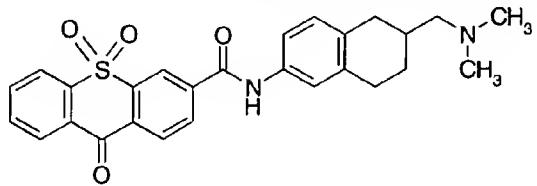


Melting point : 224 - 226°C

Washing solvent : hexane

15 Example 7

N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-9,10,10-trioxo-9,10-dihydro-10<sup>1</sup>-thioxanthene-3-carboxamide



Melting point : 222 - 223°C (decomposition)

20 Washing solvent: hexane

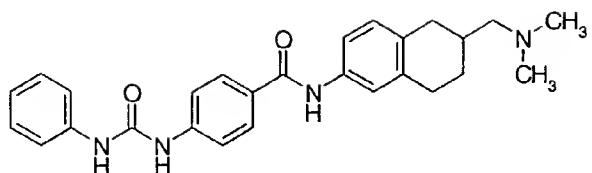
**Example 8**

(4-Anilinocarbonyl)amino-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide

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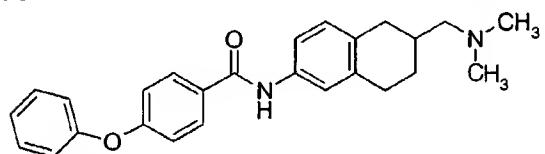


Melting point : 216 - 217°C (decomposition)

Washing solvent : hexane

## 5 Example 9

N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-4-phenoxybenzamide

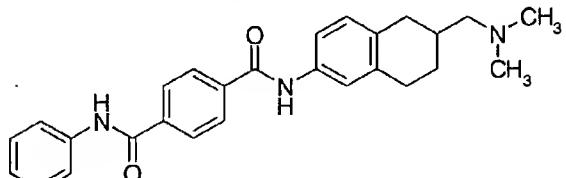


Melting point : 137 - 139°C

10 Washing solvent : hexane

## Example 10

N<sup>1</sup>-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-N<sup>4</sup>-phenylterephthalamide



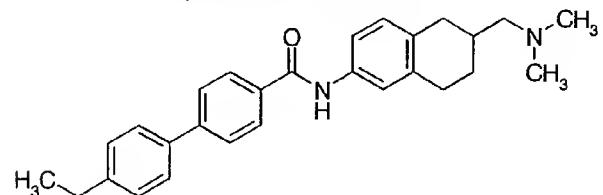
15

Melting point : 238 - 240°C (decomposition)

Washing solvent : hexane

## Example 11

20 (4'-Ethylbiphenyl-4-yl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]carboxamide



Melting point : 137 - 138°C

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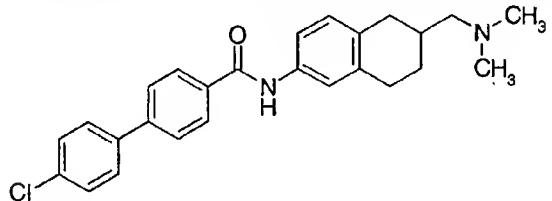
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Washing solvent : hexane

Example 12

(4'-Chlorobiphenyl-4-yl)-N-[2-(N,N-

5 dimethylamino)methyl-6-tetralinyl]carboxamide



Melting point : 187 - 189°C

Washing solvent : hexane

10 Example 13

(4'-Acetylaminobiphenyl-4-yl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]carboxamide

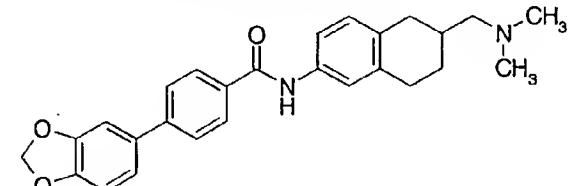


Melting point : 183 - 186°C

15 Washing solvent : hexane

Example 14

4-(1,3-Benzodioxol-5-yl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide



20 Melting point : 174 - 176°C

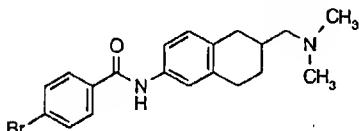
Washing solvent : hexane

Example 15

25 4-Bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-

## tetrahydro-2-naphthalenyl]benzamide

The titled compound was obtained as a white powder by the same method as in Example 1.



5 Melting point: 141 - 143°C (washing solvent: n-hexane)

## Example 16

3',4'-Dichloro-N-[6-[(N,N-dimethylamino)methyl]-

5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-

10 carboxamide



4-Bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (400 mg, 1.03 mmol) obtained in Example 15, 3,4-dichlorophenylboric acid (50 15 wt% THF-H<sub>2</sub>O solution, 0.473 ml, 1.24 mmol), and 2N sodium carbonate solution (1.03 ml, 2.07 mmol) were dissolved in 50 ml of dimethoxyethane, then palladium tetrakis(triphenylphosphine) (35.8 mg, 0.031 mmol) was added under nitrogen atmosphere, which was stirred at 90°C for 20 15 hours.

Ethyl acetate was added to the reaction mixture, which was washed with saturated aqueous sodium chloride solution, dried using anhydrous magnesium sulfate, and the solvent was distilled out under reduced pressure. The residue was 25 refined by alumina column chromatography (development solvent: n-hexane:ethyl acetate = 3:1), and pulverized with n-hexane to give the titled compound (204 mg) a white powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.41 (1H, m), 1.95 (2H, m), 2.26 (6H, s), 30 2.26-2.45 (3H, m), 2.83-2.99 (3H, m), 7.10 (1H, d, J=8.1 Hz), 7.26-7.77 (8H, m), 7.94 (2H, d, J=8.4 Hz).

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Elemental analysis for C<sub>26</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>2</sub>O · 0.1H<sub>2</sub>O

Calcd. : C, 68.60; H, 5.80; N, 6.15.

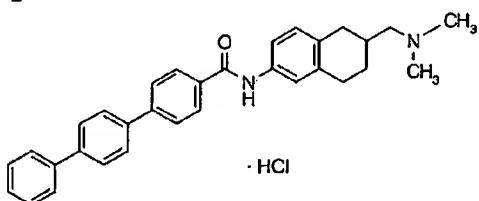
Found : C, 68.42; H, 5.60; N, 5.92.

Melting point: 143 - 145°C (crystallization solvent:  
5 ethyl acetate-hexane)

## Example 17

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-phenyl[1,1'-biphenyl]-4-carboxamide

10 hydrochloride



The free basic substance (35 mg) of the titled compound was obtained in the same manner as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-

15 tetrahydro-2-naphthalenyl]benzamide (400 mg, 1.03 mmol) obtained in Example 15, and 4-biphenylboric acid (1.25 g, 1.25 mmol). The resulting free basic substance (30 mg) was dissolved in 10 ml of methanol, then 100 ml of 1N hydrochloric acid was added, and the reaction mixture was 20 stirred. The reaction mixture was concentrated, and pulverized using diethyl ether, to give the titled compound (35.3 mg) as a white powder.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, free base) δ : 1.32 (1H, m), 1.93 (2H, m), 2.15 (6H, s), 2.15-2.36 (3H, m), 2.74-2.94 (3H, m), 7.05 (1H, d, J=8.4 Hz), 7.40-7.55 (5H, m), 7.73-7.91 (8H, m), 8.07 (2H, d, J=8.4 Hz), 10.14 (1H, s).Elemental analysis for C<sub>32</sub>H<sub>32</sub>N<sub>2</sub>O · HCl · 2H<sub>2</sub>O

Calcd. : C, 72.10; H, 7.00; N, 5.25.

Found : C, 71.81; H, 6.57; N, 5.08.

30 Melting point: 220°C (decomposition) (crystallization solvent: methanol-diethyl ether)

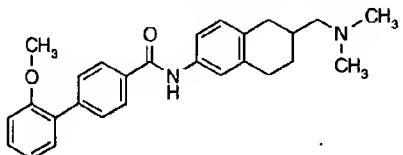
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## Example 18

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-2'-methoxy[1,1'-biphenyl]-4-carboxamide



5 The titled compound (208 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 2-methoxyphenylboric acid (118 mg, 0.775 mmol).

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.42 (1H, m), 1.96 (2H, m), 2.23 (6H, s), 2.23-2.47 (3H, m), 2.85 (3H, m), 3.83 (3H, s), 7.05 (3H, m), 7.34 (3H, m), 7.47 (1H, s), 7.64 (2H, d, J=8.4 Hz), 7.79 (1H, s), 7.90 (2H, d, J=8.4 Hz).

15 Elemental analysis for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub> • 0.1H<sub>2</sub>O  
Calcd.: C, 77.89; H, 7.31; N, 6.73.

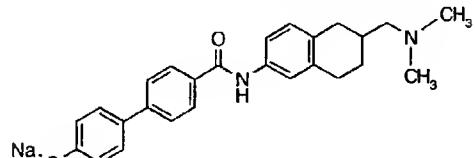
Found: C, 77.86; H, 7.18; N, 6.79.

Melting point: 155 - 157°C (crystallization solvent:  
ethyl acetate-hexane)

20

## Example 19

Sodium salt of N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-oxy[1,1'-biphenyl]-4-carboxamide



25

The titled compound (117 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol)

30 and 4-hydroxyphenylboric acid (107 mg, 0.775 mmol).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.36 (1H, m), 1.89 (2H, m), 2.15 (6H, s), 2.15-2.35 (3H, m), 2.77 (3H, m), 6.88 (2H, d, J=8.4 Hz), 7.02 (1H, d, J=8.4 Hz), 7.48 (1H, d, J=8.4 Hz), 7.53 (1H, s), 7.59 (2H, d, J=8.4 Hz), 7.73 (2H, d, J=8.4 Hz), 8.00 (2H, d, J=8.4 Hz), 10.07 (1H, s).

Elemental analysis for  $C_{26}H_{27}N_2O_2Na \cdot 0.2H_2O$

Calcd. : C, 73.29; H, 6.48; N, 6.59.

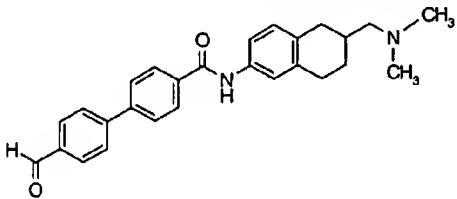
Found : C, 73.25; H, 6.18; N, 6.36.

Melting point: 246 - 248°C (crystallization solvent:

10 ethyl acetate-diethyl ether)

### Example 20

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-formyl[1,1'-biphenyl]-4-carboxamide



15            The titled compound (205 mg) was obtained as a white  
powder by the same method as in Example 16, using 4-  
bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-  
tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol)  
20 and 4-formylphenylboric acid (145 mg, 0.968 mmol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.41 (1H, m), 1.95 (2H, m), 2.26 (6H, s), 2.26-2.42 (3H, m), 2.85-2.94 (3H, m), 7.09 (2H, d, J=8.1 Hz), 7.32 (1H, d, J=8.4 Hz), 7.47 (1H, m), 7.63-7.94 (3H, m), 7.87-7.99 (4H, m), 8.13 (1H, s), 10.11 (1H, s).

25 Elemental analysis for  $C_{27}H_{28}N_2O_2 \cdot 0.2H_2O$

Calcd. : C, 77.93; H, 6.88; N, 6.73.

Found : C, 77.89; H, 6.75; N, 6.71.

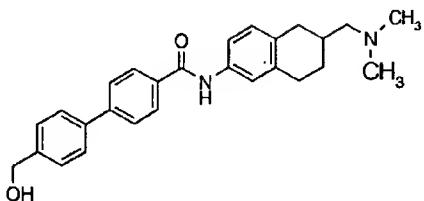
Melting point: 130 - 132° C (crystallization solvent: ethyl acetate-diethyl ether)

30

### Example 21

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-

naphthalenyl]-4'--(hydroxymethyl)[1,1'-biphenyl]-4-carboxamide



N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-  
5 tetrahydro-2-naphthalenyl]-4'-formyl[1,1'-biphenyl]-4-  
carboxamide (100 mg, 0.242 mmol) was dissolved in  
tetrahydrofuran-methanol (1:1) solution (2.4 ml), then  
sodium borohydride (18.3 mg, 0.485 mmol) was added, which  
was stirred for 2 hours. Ethyl acetate was added to the  
10 reaction mixture, which was washed with saturated aqueous  
sodium chloride solution, dried using anhydrous magnesium  
sulfate, and the solvent was distilled out under reduced  
pressure. The residue was pulverized using ether-n-  
hexane, to give the titled compound (86 mg) as a white  
15 powder.

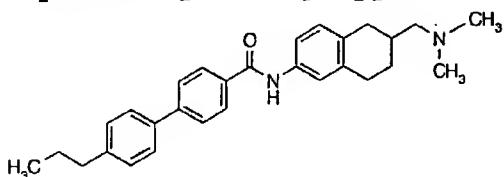
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.39 (1H, m), 1.94 (2H, m), 2.25 (6H, s),  
2.25-2.44 (3H, m), 2.82-2.95 (3H, m), 4.78 (2H, s), 7.07  
(1H, d, J=8.4 Hz), 7.31 (1H, d, J=8.4 Hz), 7.38-7.56 (4H,  
m), 7.64-7.70 (3H, m), 7.85 (1H, s), 7.93 (2H, d, J=8.4 Hz).  
20 Elemental analysis for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub> · 0.2H<sub>2</sub>O  
Calcd. : C, 77.56; H, 7.33; N, 6.70.  
Found : C, 77.53; H, 7.27; N, 6.55.

Melting point: 138 - 139° C (crystallization solvent: ethyl  
acetate-diethyl ether)

25

Example 22

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-propyl[1,1'-biphenyl]-4-carboxamide



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The titled compound (158 mg) was obtained as a white powder by the same method as in Example 1, using N-[(6-amino-1,2,3,4-tetrahydro-2-naphthalenyl)methyl]-N,N-dimethylamine (102 mg, 0.499 mmol), and 4-(4-propyl)benzoic acid (144 mg, 0.599 mmol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.98 (3H, t, J=7.5 Hz), 1.40 (1H, m), 1.69 (2H, m), 1.94 (2H, m), 2.25 (6H, s), 2.25-2.45 (3H, m), 2.64 (2H, t, J=7.5 Hz), 2.85 (3H, m), 7.08 (1H, d, J=7.8 Hz), 7.26 (3H, m), 7.46 (1H, s), 7.54 (2H, d, J=8.1 Hz), 7.67 (2H, d, J=8.1 Hz), 7.81 (1H, s), 7.91 (2H, d, J=8.4 Hz).

Elemental analysis for C<sub>29</sub>H<sub>34</sub>N<sub>2</sub>O

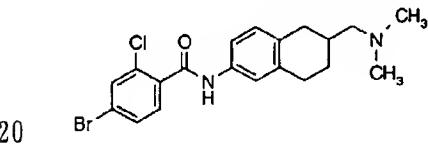
Calcd.: C, 81.65; H, 8.03; N, 6.57.

Found: C, 81.30; H, 7.94; N, 6.40.

Melting point: 186 - 188°C (crystallization solvent: ethyl acetate-diethyl ether)

### Example 23

4-Bromo-2-chloro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide



The titled compound (483 mg) was obtained as a white powder by the same method as in Example 1, using N-[(6-amino-1,2,3,4-tetrahydro-2-naphthalenyl)methyl]-N,N-dimethylamine (300 mg, 1.47 mmol) and 4-bromo-2-chloro benzoic acid (415 mg, 1.76 mmol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.40 (1H, m), 1.94 (2H, m), 2.25 (6H, s), 2.25-2.44 (3H, m), 2.94 (3H, m), 7.08 (1H, d, J=8.4 Hz), 7.28 (1H, m), 7.41 (1H, s), 7.50 (1H, m), 7.61 (2H, m), 7.81 (1H, s).

Elemental analysis for C<sub>20</sub>H<sub>22</sub>BrClN<sub>2</sub>O

Calcd.: C, 56.96; H, 5.26; N, 6.64.

Found: C, 57.09; H, 5.37; N, 6.55.

Melting point: 130 - 132°C (crystallization solvent: ethyl acetate-diethyl ether)

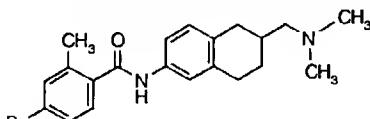
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## Example 24

4-Bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-2-methylbenzamide



5

The titled compound (418 mg) was obtained as a white powder by the same method as in Example 1, using N-[(6-amino-1,2,3,4-tetrahydro-2-naphthalenyl)methyl]-N,N-dimethylamine (293 mg, 1.43 mmol) and 4-bromo-2-methylbenzoic acid (370 mg, 1.72 mmol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.40 (1H, m), 2.04 (2H, m), 2.25 (6H, s), 2.25-2.40 (3H, m), 2.46 (3H, s), 2.88 (3H, m), 7.07 (1H, d, J=7.8 Hz), 7.21-7.41 (6H, m).

Elemental analysis for C<sub>21</sub>H<sub>25</sub>BrN<sub>2</sub>O

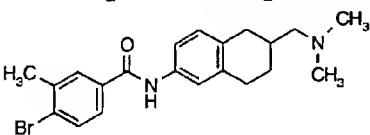
15 Calcd. : C, 62.85; H, 6.28; N, 6.98.

Found : C, 63.10; H, 6.11; N, 6.97.

Melting point: 140 - 142°C (crystallization solvent: ethyl acetate-hexane)

## 20 Example 25

4-Bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-3-methylbenzamide



25 The titled compound (434 mg) was obtained as a white powder by the same method as in Example 1, using N-[(6-amino-1,2,3,4-tetrahydro-2-naphthalenyl)methyl]-N,N-dimethylamine (300 mg, 1.47 mmol) and 4-bromo-3-methylbenzoic acid (379 mg, 1.76 mmol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.40 (1H, m), 1.93 (2H, m), 2.25 (6H, s),

30 2.25-2.40 (3H, m), 2.46 (3H, s), 2.87 (3H, m), 7.07 (1H, d, J=7.8 Hz), 7.29 (1H, m), 7.40 (1H, s), 7.49 (1H, m), 7.61 (1H, d, J=8.1 Hz), 7.72 (2H, s-like).

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Elemental analysis for C<sub>21</sub>H<sub>25</sub>BrN<sub>2</sub>O

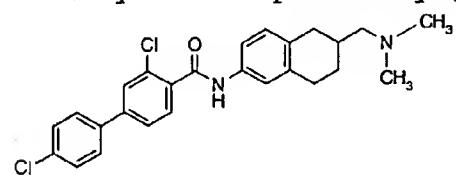
Calcd.: C, 62.85; H, 6.28; N, 6.98.

Found: C, 62.84; H, 6.05; N, 6.93.

Melting point: 154 - 155°C (crystallization solvent: ethyl  
5 acetate-hexane)

## Example 26

3,4'-Dichloro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



10

The titled compound (122 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-2-chloro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.607 mmol) obtained in Example 23, and 4-chlorophenyl boric acid (114 mg, 0.729 mmol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.41 (1H, m), 1.95 (2H, m), 2.26 (6H, s), 2.26-2.42 (3H, m), 2.85 (3H, m), 7.10 (1H, d, J=8.4 Hz), 7.31 (1H, m), 7.43-7.63 (8H, m), 7.87 (1H, d, J=8.1 Hz).

15

Elemental analysis for C<sub>26</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>2</sub>O

Calcd.: C, 68.87; H, 5.78; N, 6.18.

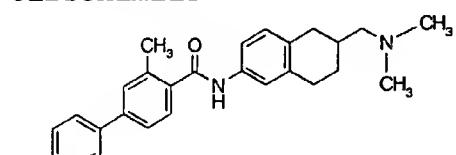
Found: C, 68.61; H, 5.49; N, 6.10.

Melting point: 177 - 179°C (crystallization solvent: ethyl acetate-diethyl ether)

20

## Example 27

4'-Chloro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-3-methyl[1,1'-biphenyl]-4-carboxamide



25

30

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The titled compound (129 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-2-methylbenzamide (250 mg, 0.623 mmol) obtained in Example 24, and 4-chlorophenylboric acid (117 mg, 0.747 mmol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.42 (1H, m), 1.96 (2H, m), 2.37 (6H, s), 2.37-2.47 (3H, m), 2.56 (3H, s), 2.90 (3H, m), 7.08 (1H, d, J=8.1 Hz), 7.26 (1H, m), 7.41 (6H, m), 7.53 (3H, m).

Elemental analysis for C<sub>27</sub>H<sub>29</sub>ClN<sub>2</sub>O · H<sub>2</sub>O

Calcd.: C, 71.90; H, 6.93; N, 6.21.

Found: C, 71.92; H, 6.52; N, 5.92.

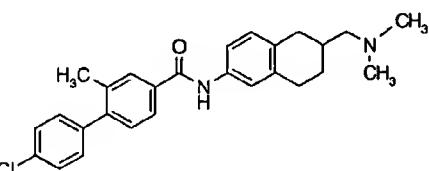
Melting point: 163 - 165° C (crystallization solvent: ethyl acetate-diethyl ether)

15

### Example 28

4'-Chloro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-2-methyl[1,1'-biphenyl]-4-carboxamide

20



The titled compound (168 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-3-methylbenzamide (250 mg, 0.623 mmol) obtained in Example 25, and 4-chlorophenylboric acid (117 mg, 0.747 mmol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.41 (1H, m), 1.95 (2H, m), 2.26 (6H, s), 2.24-2.42 (3H, m), 2.33 (3H, s), 2.85 (3H, m), 7.09 (1H, d, J=8.4 Hz), 7.26 (4H, m), 7.43 (3H, m), 7.73 (3H, m).

Elemental analysis for C<sub>27</sub>H<sub>29</sub>ClN<sub>2</sub>O · 0.2H<sub>2</sub>O

Calcd.: C, 74.28; H, 6.79; N, 6.42.

Found: C, 74.27; H, 6.73; N, 6.27.

Melting point: 193 - 195° C (crystallization solvent: ethyl

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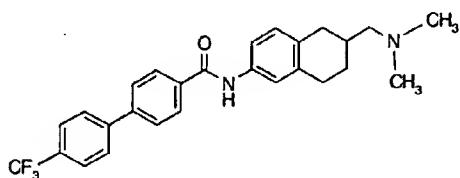
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acetate-diethyl ether)

## Example 29

5 N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-(trifluoromethyl)[1,1-biphenyl]-4-carboxamide



The titled compound (194 mg) was obtained as a white powder by the same method as in Example 16, using 4-  
10 bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 4-trifluoromethylphenylboric acid (147 mg, 0.775 mmol).

15  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.41 (1H, m), 1.95 (2H, m), 2.25 (6H, s), 2.25-2.45 (3H, m), 2.89 (3H, m), 7.09 (1H, d,  $J=8.1$  Hz), 7.31 (1H, d,  $J=8.1$  Hz), 7.46 (1H, s), 7.70 (6H, m), 7.80 (1H, m), 7.96 (2H, d,  $J=8.4$  Hz).

Elemental analysis for  $\text{C}_{27}\text{H}_{27}\text{F}_3\text{N}_2\text{O}$

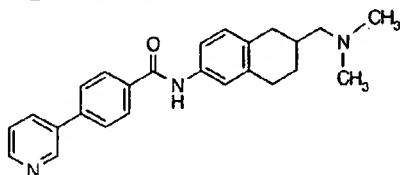
Calcd.: C, 71.66; H, 6.01; N, 6.19.

20 Found: C, 71.44; H, 6.05; N, 6.09.

Melting point: 205 - 206°C (crystallization solvent: ethyl acetate-diisopropyl ether)

## Example 30

25 N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4-(3-pyridinyl)benzamide



The titled compound (194 mg) was obtained as a white powder by the same method as in Example 16, using 4-  
30 bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-

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tetrahydro-2-naphthalenyl)benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 2-(3-pyridyl)-1,3,2,-dioxaborinane (126 mg, 0.775 mmol).

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.41 (1H, m), 1.95 (2H, m), 2.26 (6H, s), 2.26-2.42 (3H, m), 2.85 (3H, m), 7.09 (1H, d,  $J=7.8$  Hz), 7.30-7.47 (3H, m), 7.69 (2H, d,  $J=8.4$  Hz), 7.86-7.99 (4H, m), 8.64 (1H, m), 8.87 (1H, m).

Elemental analysis for  $\text{C}_{25}\text{H}_{24}\text{N}_3\text{O} \cdot 0.1\text{H}_2\text{O}$

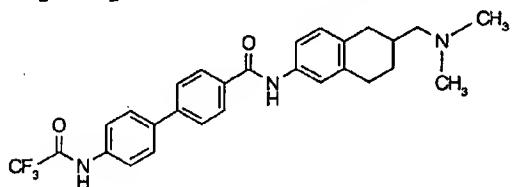
Calcd.: C, 77.53; H, 7.08; N, 10.85.

10 Found: C, 77.42; H, 7.05; N, 10.58.

Melting point: 177 - 178°C (crystallization solvent: ethyl acetate-diisopropyl ether)

### Example 31

15 N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-'-[(trifluoroacetyl)amino][1,1'-biphenyl]-4-carboxamide



20 The titled compound (1.02 g) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (1.00 g, 2.58 mmol) obtained in Example 15, and 4-trifluoroacetamidophenylboric acid (722 mg, 3.10 mmol).

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.41 (1H, m), 2.05 (2H, m), 2.26 (6H, s), 2.26-2.42 (3H, m), 2.89 (3H, m), 7.09 (1H, d,  $J=8.4$  Hz), 7.29 (2H, m), 7.46 (1H, s), 7.69 (7H, m), 7.94 (2H, d,  $J=8.1$  Hz).

Elemental analysis for  $\text{C}_{28}\text{H}_{28}\text{F}_3\text{N}_3\text{O}_2$

30 Calcd.: C, 67.87; H, 5.70; N, 8.48.

Found: C, 67.70; H, 5.53; N, 8.42.

Melting point: 235 - 237°C (crystallization solvent: ethyl

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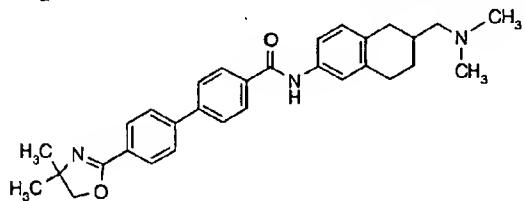
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acetate-diisopropyl ether)

## Example 32

5      N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)[1,1'-biphenyl]-4-carboxamide



The titled compound (238 mg) was obtained as a white powder by the same method as in Example 16, using 4-

10. bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 4-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)phenylboronic acid (170 mg, 0.775 mmol).

15      $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.41 (7H, m), 1.94 (2H, m), 2.25 (6H, s), 2.25-2.41 (3H, m), 2.84 (3H, m), 4.14 (2H, s), 7.08 (1H, d,  $J=7.8$  Hz), 7.30 (1H, m), 7.46 (1H, s), 7.68 (5H, m), 7.94 (2H, d,  $J=8.4$  Hz), 8.03 (2H, d,  $J=8.4$  Hz).

Elemental analysis for  $\text{C}_{31}\text{H}_{35}\text{N}_3\text{O}_2 \cdot 0.2\text{H}_2\text{O}$

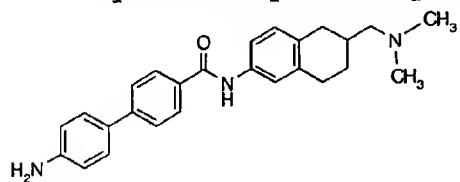
20     Calcd.: C, 76.74; H, 7.35; N, 8.66.

Found: C, 76.70; H, 7.19; N, 8.49.

Melting point: 185 - 187°C (crystallization solvent: ethyl acetate-diisopropyl ether)

## 25    Example 33

4'-Amino-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-

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tetrahydro-2-naphthalenyl]-4'-[(trifluoroacetyl)amino][1,1'-biphenyl]-4-carboxamide (850 mg, 1.72 mmol) obtained in Example 31 was suspended in a mixed solution of methanol (8 ml) and tetrahydrofuran (4 ml), then 1N sodium hydroxide (3.4 ml) was added, which was stirred at 50° C for 16 hours. The solvent was distilled out under reduced pressure, and the residue was pulverized using water, to give the titled compound (685 mg) as a white powder.

10     <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.31 (1H, m), 1.89 (2H, m), 2.15 (6H, s), 2.15-2.34 (3H, m), 2.83 (3H, m), 5.36 (2H, s), 6.67 (2H, d, J=8.4 Hz), 7.03 (1H, d, J=8.1 Hz), 7.48 (4H, m), 7.68 (2H, d, J=8.1 Hz), 7.96 (2H, d, J=8.4 Hz), 10.02 (1H, s). Elemental analysis for C<sub>26</sub>H<sub>29</sub>N<sub>3</sub>O · 1.1H<sub>2</sub>O

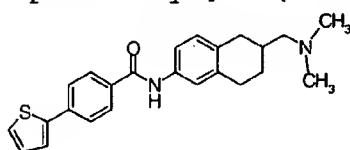
15     Calcd.: C, 74.47; H, 7.50; N, 10.02.

      Found: C, 74.39; H, 7.41; N, 9.82.

Melting point: 148 - 150° C (crystallization solvent:  
methanol-water)

20     Example 34

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4-(2-thienyl) benzamide



25     The titled compound (70 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 2-thienylboric acid (99.1 mg, 0.775 mmol).

30     <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.41 (1H, m), 1.94 (2H, m), 2.25 (6H, s), 2.25-2.45 (3H, m), 2.89 (3H, m), 7.11 (2H, m), 7.29-7.45 (4H, m), 7.71 (3H, m), 7.87 (2H, d, J=8.4 Hz).

Elemental analysis for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>OS

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Calcd. : C, 73.81; H, 6.71; N, 7.17.

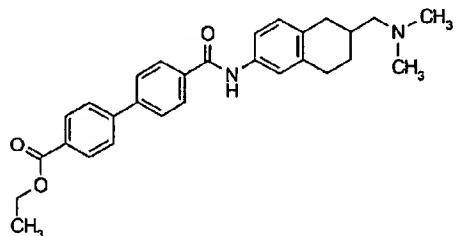
Found : C, 73.49; H, 6.59; N, 7.14.

Melting point: 165 - 166° C (crystallization solvent: ethyl acetate-diisopropyl ether)

5

## Example 35

Ethyl 4'-[[[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]amino]carbonyl][1,1'-biphenyl]-4-carboxylate



10

The titled compound (202 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 4-ethoxycarbonylphenylboric acid (150 mg, 0.775 mmol).

15

1H-NMR (CDCl<sub>3</sub>) δ: 1.42 (4H, m), 1.95 (2H, m), 2.26 (6H, s), 2.26-2.42 (3H, m), 2.89 (3H, m), 4.41 (2H, q, J=7.2 Hz), 7.09 (1H, d, J=8.4 Hz), 7.31 (1H, d, J=8.4 Hz), 7.47 (1H, s), 7.70 (4H, m), 7.80 (1H, s), 7.96 (2H, d, J=8.4 Hz), 8.14 (2H, d, J=8.4 Hz).

20

Elemental analysis for C<sub>29</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>

Calcd. : C, 76.29; H, 7.06; N, 6.14.

Found : C, 76.25; H, 7.07; N, 6.09.

25

Melting point: 156 - 158° C (crystallization solvent: ethyl acetate-diisopropyl ether)

## Example 36

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-(methylsulfanyl)[1,1'-biphenyl]-4-carboxamide

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The titled compound (360 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (500 mg, 1.29 mmol) obtained in Example 15, and 4-methylthiophenylboric acid (260 mg, 1.55 mmol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.41 (1H, m), 1.94 (2H, m), 2.26 (6H, s), 2.26-2.42 (3H, m), 2.53 (3H, s), 2.94 (3H, m), 7.09 (1H, d, J=8.1 Hz), 7.29-7.36 (3H, m), 7.46 (1H, s), 7.56 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=8.1 Hz), 7.78 (1H, m), 7.92 (2H, d, J=9.0 Hz).

Elemental analysis for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>OS · 0.2H<sub>2</sub>O

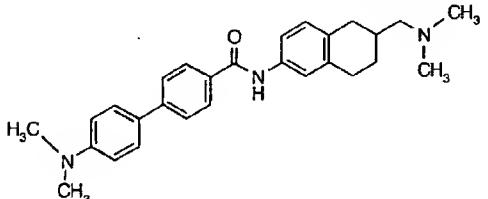
Calcd. : C, 74.69; H, 7.04; N, 6.45.

15 Found : C, 74.63; H, 7.03; N, 6.11.

Melting point: 178 - 180°C (crystallization solvent: ethyl acetate-diisopropyl ether)

#### Example 37

20 4'-(N,N-Dimethylamino)-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



25 4'-Amino-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide (150 mg, 0.375 mmol) obtained in Example 33, and paraformaldehyde (45.1 mg, 1.50 mmol) were suspended in mixed solution of methanol (1 ml) and tetrahydrofuran (1 ml). Sodium cyanohydroborate (94.4 mg, 1.50 mmol) was

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added to the reaction mixture, which was stirred at 40° C for 18 hours. Ethyl acetate was added to the reaction mixture, which was washed with saturated aqueous sodium chloride solution, dried using anhydrous magnesium

5 sulfate, and the solvent was distilled out under reduced pressure. The residue was refined using alumina column chromatography (development solvent; ethyl acetate), and pulverized using isopropyl ether, to give the titled compound (13 mg) as a white powder.

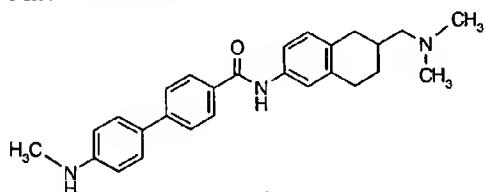
10  $^1\text{H-NMR}$  (DMSO- $\text{d}_6$ )  $\delta$  : 1.32 (1H, m), 1.90 (2H, m), 2.15 (6H, s), 2.15-2.35 (3H, m), 2.77 (3H, m), 2.97 (6H, s), 6.82 (2H, d, J=8.4 Hz), 7.03 (1H, d, J=8.4 Hz), 7.48 (1H, d, J=8.1 Hz), 7.53 (1H, s), 7.63 (2H, d, J=8.7 Hz), 7.74 (2H, d, J=7.8 Hz), 7.98 (2H, d, J=8.4 Hz), 10.04 (1H, s).

15 FABMS(pos) 428.2[M+H] $^+$

Melting point: 212 - 213° C (crystallization solvent: ethyl acetate-diisopropyl ether)

#### Example 38

20 N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-(methylamino)[1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as a white powder by 25 the same method as in Example 37, using 4'-amino-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl] [1,1'-biphenyl]-4-carboxamide (150 mg, 0.375 mmol) obtained in Example 33, paraformaldehyde (15.0 mg, 0.50 mmol), and sodium cyanohydroborate (31.5 mg, 0.50 mmol).

30  $^1\text{H-NMR}$  (DMSO- $\text{d}_6$ )  $\delta$  : 1.32 (1H, m), 1.89 (2H, m), 2.15 (6H, s), 2.15-2.31 (3H, m), 2.72 (7H, m), 5.94 (1H, m), 6.64 (2H,

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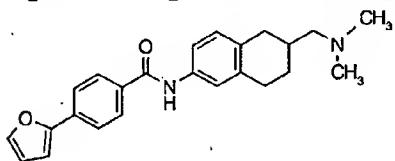
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d, J=9.0 Hz), 7.03 (1H, d, J=8.7 Hz), 7.49 (4H, m), 7.70 (1H, d, J=8.4 Hz), 7.97 (2H, d, J=8.4 Hz), 10.02 (1H, s).  
FABMS(pos) 414.3[M+H]<sup>+</sup>

Melting point: 163 - 165°C (crystallization solvent: ethyl acetate-diisopropyl ether)

5 Example 39

N-[6-[(N,N-Dimethyl)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4-(2-furyl)benzamide



10

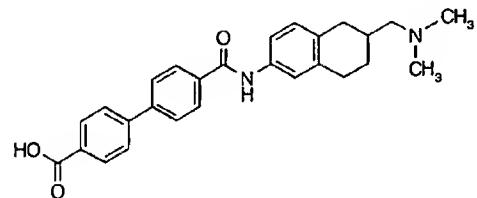
The titled compound (67 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethyl)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 2-furylboric acid (86.7 mg, 0.775 mmol).  
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.40 (1H, m), 1.94 (2H, m), 2.25 (6H, s), 2.25-2.45 (3H, m), 2.88 (3H, m), 7.08 (1H, d, J=8.1 Hz), 7.26 (4H, m), 7.41 (1H, m), 7.60-7.74 (5H, m).

FABMS(pos) 375.2[M+H]<sup>+</sup>

15

Example 40

4'-[[[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]amino]carbonyl][1,1'-biphenyl]-4-carboxylic acid



20

Ethyl-4'-[[[6-[(N,N-dimethyl)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]amino]carbonyl][1,1'-biphenyl]-4-carboxylate (100 mg, 0.219 mmol) obtained in Example 35 was dissolved in a mixed solution of ethanol (3

25

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ml) and water (0.5 ml). 1N aqueous sodium hydroxide solution (0.329 ml) was added to the reaction mixture at room temperature, which was stirred at 90° C for 5 hours.

After the solvent was distilled out under reduced pressure, water was added to the residue, then 1N hydrochloric acid (0.329 ml) was added and the reaction mixture was stirred. The precipitated crude product collected by filtration, and washed with water to give the titled compound (89 mg) as a white powder.

10  $^1\text{H-NMR}$  (DMSO-d<sub>6</sub>)  $\delta$ : 1.34 (1H, m), 1.91 (2H, m), 2.24 (6H, s), 2.24-2.30 (3H, m), 2.81 (3H, m), 7.05 (1H, d, J=8.4 Hz), 7.49 (1H, d, J=8.4 Hz), 7.55 (1H, s), 7.89 (4H, m), 8.07 (4H, m), 10.18 (1H, s).

Elemental analysis for C<sub>27</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub> · 2H<sub>2</sub>O

15 Calcd.: C, 69.81; H, 6.94; N, 6.03.

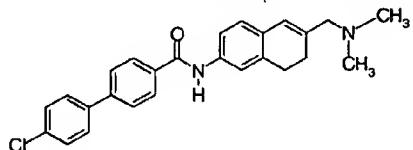
Found: C, 69.57; H, 7.01; N, 5.93.

Melting point: 143° C (decomposition) (crystallization solvent: water)

20

#### Example 41

4'-Chloro-N-[6-[(N,N-dimethyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



25 1) 6-Acetamido-1-tetralone (5.0 g, 0.0246 mol) synthesized according to a known method by documents (*Journal of Organic Chemistry* 27, 70 (1962)), was dissolved in 50 ml of DMF dimethylacetal, which was stirred at 110° C for 2 hours. The precipitate was collected by filtration, 30 and washed with ethyl acetate to give 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone (4.98 g) as a yellow powder.

$^1\text{H-NMR}$  (CDCl<sub>3</sub>)  $\delta$ : 2.19 (3H, s), 2.79-2.83 (2H, m), 2.88-

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2.92 (2H, m), 3.11 (6H, s), 7.14-7.17 (1H, m), 7.68 (1H,

s), 7.69 (1H, s), 7.95 (1H, d, J=8.1Hz), 7.96 (1H, s).

Melting point: 207 - 210°C (crystallization solvent: ethyl acetate)

5        2) The obtained 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone (4.50 g, 0.0173 mol) was dissolved in methanol (50 ml), and sodium borohydride (6.56 g, 0.173 mol) was added to the solution under ice-cooling, which was stirred for 2 hours. The 10 reaction mixture was concentrated. Ethyl acetate and sodium hydrogencarbonate solution were added to the residue, and extraction was conducted. The ethyl acetate layer was concentrated, and 30 ml of tetrahydrofuran and 30 ml of 2N hydrochloric acid were added to the residue, 15 which was refluxed with heating for 16 hours. The reaction mixture was concentrated, and ethyl acetate and 2N sodium hydroxide solution were added, and extraction was conducted. The ethyl acetate layer was concentrated, and the residue was refined using alumina column chromatography 20 (development solvent; ethyl acetate:n-hexane = 30:70), to give 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthaleneamine (1.60 g) as a colorless oily substance. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.23 (6H, s), 2.28 (2H, t, J=8.4Hz), 2.74 (2H, t, J=8.4Hz), 2.95 (2H, s), 3.57-3.72 (2H, m), 6.25 (1H, s), 6.46-6.48 (2H, m), 6.83 (1H, d, J=8.7Hz).

3) The titled compound (1.12 g) was obtained as a white powder by the same method as in Example 1, using the obtained 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine (1.00 g, 0.005 mol), and 4-chlorobiphenyl 30 carboxylic acid (2.31 g, 0.01 mol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.25 (6H, s), 2.34 (2H, t, J=7.8Hz), 2.86 (2H, t, J=7.8Hz), 2.99 (2H, s), 6.34 (1H, s), 7.03 (1H, d, J=8.7Hz), 7.39 (1H, d, J=8.1 Hz), 7.45 (2H, d, J=8.7), 7.48 (1H, s), 7.56 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=8.4 Hz), 35 7.78 (1H, s), 7.94 (2H, d, J=8.4 Hz).

Elemental analysis for C<sub>26</sub>H<sub>25</sub>ClN<sub>2</sub>O

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Calcd. : C, 74.90; H, 6.04; N, 6.72.

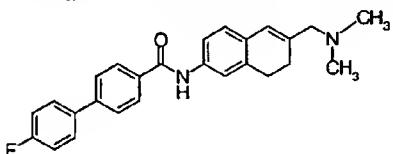
Found : C, 74.64; H, 6.14; N, 6.56.

Melting point: 204 - 207° C (crystallization solvent: ethyl acetate - n-hexane)

5

## Example 42

4'-Fluoro-N-[6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



10 The titled compound (990 mg) was obtained as a white powder by the same method as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine (936 mg, 4.62 mmol) obtained in Example 41-2), and 4-fluorobiphenylcarboxylic acid (1.00 g, 4.62 mmol).

15  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.25 (6H, s), 2.34 (2H, t,  $J=8.1\text{Hz}$ ), 2.85 (2H, t,  $J=8.1\text{Hz}$ ), 2.99 (2H, s), 6.34 (1H, s), 7.02 (1H, d,  $J=8.1\text{Hz}$ ), 7.13-7.19 (2H, m), 7.38-7.41 (1H, m), 7.48 (1H, s), 7.56-7.61 (2H, m), 7.65 (2H, d,  $J=8.4\text{ Hz}$ ), 7.80 (1H, s), 7.93 (2H, d,  $J=8.5\text{Hz}$ ).

Elemental analysis for  $\text{C}_{26}\text{H}_{25}\text{FN}_2\text{O}$ 

Calcd. : C, 77.97; H, 6.29; N, 6.99.

Found : C, 77.90; H, 6.23; N, 6.58.

20 Melting point: 190 - 193° C (crystallization solvent: ethyl acetate - n-hexane)

25

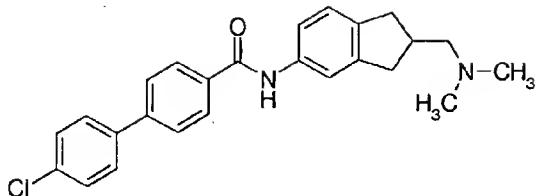
## Example 43

4'-Chloro-N-[2-[(dimethylamino)methyl]-2,3-dihydro-1H-inden-5-yl][1,1'-biphenyl]-4-carboxamide

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Concentrated hydrochloric acid (1 ml) was added to N-[2-[(dimethylamino)methyl]-2,3-dihydro-1H-inden-5-yl]acetamide (48.9 mg, 0.210 mmol) obtained in Reference Example 48, which was stirred at 110°C for 2 hours, and the solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with potassium carbonate solution and saturated aqueous sodium chloride solution, dried using anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. Using the oily substance obtained, the same operation as in Example 1 was conducted to give the titled compound (30 mg).

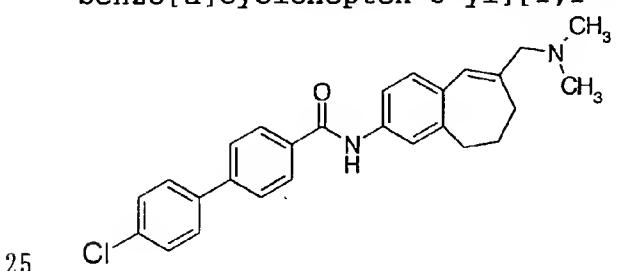
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ : 2.16 (6H, s), 2.22 (2H, d, J = 6.7 Hz), 2.61 (4H, m), 2.97 (1H, m), 7.15 (1H, d, J = 8.1 Hz), 7.47 (1H, d, J = 8.1 Hz), 7.56 (2H, d, J = 8.4 Hz), 8.05 (2H, d, J = 8.4 Hz), 10.17 (1H, s).

FAB(pos) 405.1 [M+H]<sup>+</sup>

Melting point: 192 - 194°C (crystallization solvent: ethyl acetate - diisopropyl ether)

#### Example 44

4'-Chloro-N-[8-[(dimethylamino)methyl]-6,7-dihydro-5H-benzo[a]cyclohepten-3-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 8-

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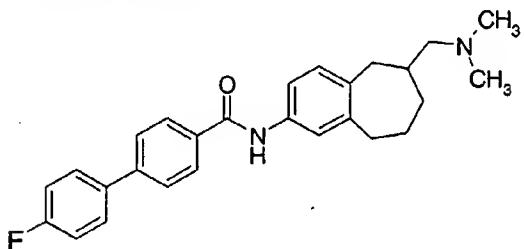
[(dimethylamino)methyl]-6,7-dihydro-5H-benzo[a]cyclohepten-3-amine obtained in Reference Example 50.

5       <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.96-2.10 (2H, m), 2.25 (6H, s), 2.39 (2H, t, J = 6.4 Hz), 2.79-2.85 (2H, m), 2.96 (2H, s), 6.40 (1H, s), 7.15 (1H, d, J = 8.6Hz), 7.40-7.52 (4H, m), 7.56 (2H, d, J = 8.4Hz), 7.67 (2H, d, J = 8.1Hz), 7.81 (1H, s), 7.94 (2H, d, J = 8.1 Hz).

Melting point: 183-185°C (crystallization solvent: ethyl 10 acetate - diethyl ether)

Example 45

4'-Fluoro-N-[6-[(dimethylamino)methyl]-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-yl][1,1'-biphenyl]-15 4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(dimethylamino)methyl]-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-20 amine obtained in Reference Example 51.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.40-1.68 (3H, m), 1.85-2.20 (10H, m), 2.55-2.92 (4H, m), 7.13-7.20 (3H ,m), 7.35-7.43 (2H, m), 7.56-7.67 (4H, m), 7.77 (1H, s), 7.93 (2H, d, J=8.4 Hz).

Elemental analysis for C<sub>27</sub>H<sub>29</sub>FN<sub>2</sub>O

25       Calcd. : C, 77.85; H, 7.02; N, 6.73.

Found : C, 78.18; H, 7.09; N, 6.74.

Melting point: 167 - 169°C (crystallization solvent: diethyl ether)

30       Example 46

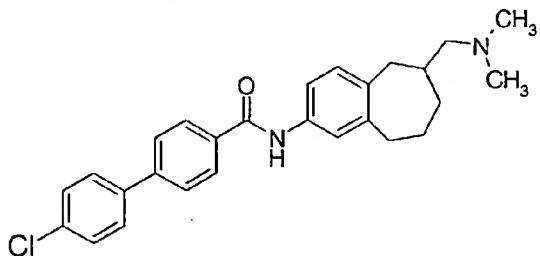
4'-Chloro-N-[6-[(dimethylamino)methyl]-6,7,8,9-

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**tetrahydro-5H-benzo[a]cyclohepten-2-yl][1,1'-biphenyl]-4-carboxamide**



The titled compound was obtained by carrying out the  
5 same operation as in Experiment Example 1, using 6-[  
[(dimethylamino)methyl]-6,7,8,9-tetrahydro-5H-  
benzo[a]cyclohepten-2-amine obtained in Reference Example  
51.

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.40-1.67 (3H, m), 1.85-2.20 (10H, m),  
2.55-2.92 (4H, m), 7.15 (1H, d,  $J$  = 8.1 Hz), 7.35-7.46 (4H,  
m), 7.56 (2H, d,  $J$  = 8.4 Hz), 7.66 (2H, d,  $J$  = 8.1 Hz), 7.77  
(1H, s), 7.93 (2H, d,  $J$  = 8.4 Hz).

Elemental analysis for  $\text{C}_{27}\text{H}_{29}\text{ClN}_2\text{O}$

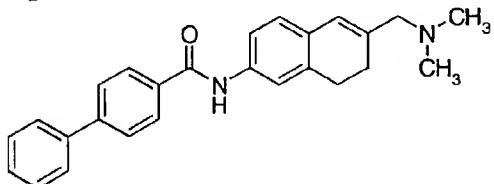
Calcd.: C, 74.90; H, 6.75; N, 6.47.

15 Found: C, 74.77; H, 6.65; N, 6.43.

Melting point: 173 - 175°C (crystallization solvent:  
diethyl ether)

**Example 47**

20 N-[6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the  
same operation as in Example 1, using 6-[(N,N-  
25 dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine  
obtained in Example 41-2).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.25 (6H, s), 2.33 (2H, t,  $J$  = 5.4 Hz),

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2.84 (2H, t, J = 5.4 Hz), 2.98 (2H, s), 6.34 (1H, s), 7.01 (1H, d, J = 7.8 Hz), 7.32-7.94 (12H, m).

Elemental analysis for C<sub>26</sub>H<sub>26</sub>N<sub>2</sub>O

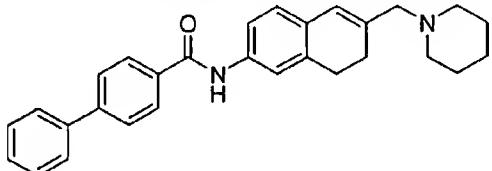
Calcd.: C, 81.64; H, 6.85; N, 7.32.

5 Found: C, 81.65; H, 6.79; N, 6.91.

Melting point: 173 - 175°C (crystallization solvent:  
tetrahydrofuran - n-hexane)

Example 48

10 N-[6-(1-Piperidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-

15 piperidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 52.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 1.46-1.59 (6H, m), 2.31-2.36 (6H, m), 2.84 (2H, t, J = 8.0 Hz), 3.02 (2H, s), 6.34 (1H, s), 7.02 (1H, d, J = 8.1 Hz), 7.37-7.50 (4H, m), 7.63 (2H, d, J = 6.9 Hz),

20 7.71 (2H, d, J = 8.1 Hz), 7.79 (1H, s), 7.94 (2H, d, J = 8.1 Hz).

Melting point: 156 - 158°C (crystallization solvent:  
tetrahydrofuran - n-hexane)

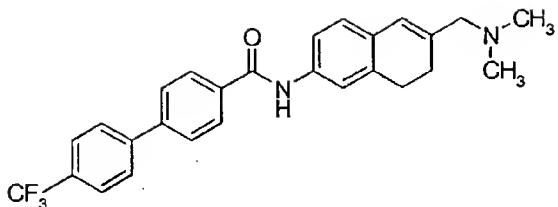
25 Example 49

N-[6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-4'-trifluoromethyl[1,1'-biphenyl]-4-carboxamide

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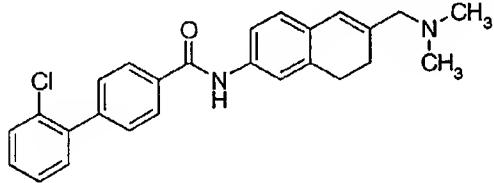
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Example 41-2).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.25 (6H, s), 2.34 (d, J = 5.1 Hz), 2.86 (2H, d, J = 5.1 Hz), 2.99 (2H, s), 6.35 (1H, s), 7.04 (1H, d, J = 8.4 Hz), 7.40 (1H, d, J = 3.3 Hz), 7.49 (1H, s), 7.70-7.79 (6H, m), 7.87 (2H, d, J = 8.4 Hz).

Melting point: 214 - 216°C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 50

2'-Chloro-N-[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Example 41-2).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.25 (6H, s), 2.34 (d, J = 5.1 Hz), 2.85 (2H, d, J = 5.1 Hz), 3.00 (2H, s), 6.34 (1H, s), 6.69 (1H, s), 7.02 (1H, d, J = 8.4 Hz), 7.31-7.57 (8H, m), 7.85 (1H, s), 7.92 (2H, d, J = 7.8 Hz).

Elemental analysis for C<sub>26</sub>H<sub>25</sub>ClN<sub>2</sub>O

Calcd.: C, 74.90; H, 6.04; N, 6.72

Found: C, 74.49; H, 5.65; N, 6.06.

Melting point: 145 - 147°C (crystallization solvent: ethyl

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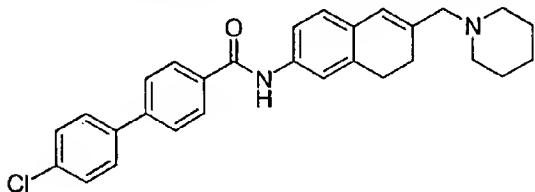
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acetate - n-hexane)

## Example 51

4'-Chloro-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



After N,N-dimethylformaldehyde solution (5 ml) of 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide (225 mg)

10 obtained in Reference Example 56, piperidine (0.16 ml), and diisopropylethylamine (0.282 ml) was stirred at room temperature for 15 hours, which was heated at 120°C for 2 hours. The residue obtained by concentrating the reaction mixture was dissolved in water-ethyl acetate, then 15 extracted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried using anhydrous magnesium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was refined using alumina column chromatography 20 (development solvent; tetrahydrofuran:n-hexane = 1:5), and crystallized using tetrahydrofuran - n-hexane to give the titled compound (110 mg).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ : 1.26-1.61 (6H, m), 2.30-2.36 (6H, m), 2.83 (2H, t, J = 8.4 Hz), 3.02 (2H, s), 6.33 (1H, s), 7.01 (1H, d, J = 8.1 Hz), 7.36-7.49 (4H, m), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.81 (1H, s), 7.93 (2H, d, J = 8.1 Hz).

Melting point: 209 - 211°C (crystallization solvent:  
tetrahydrofuran - n-hexane)

30

## Example 52

4'-Fluoro-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-